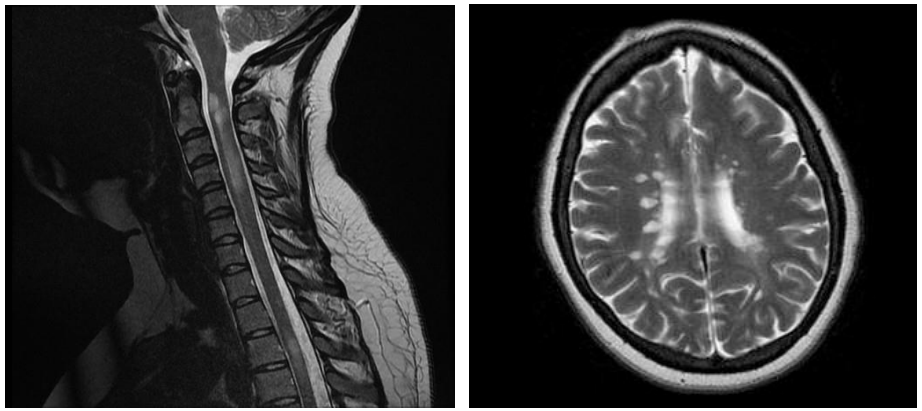
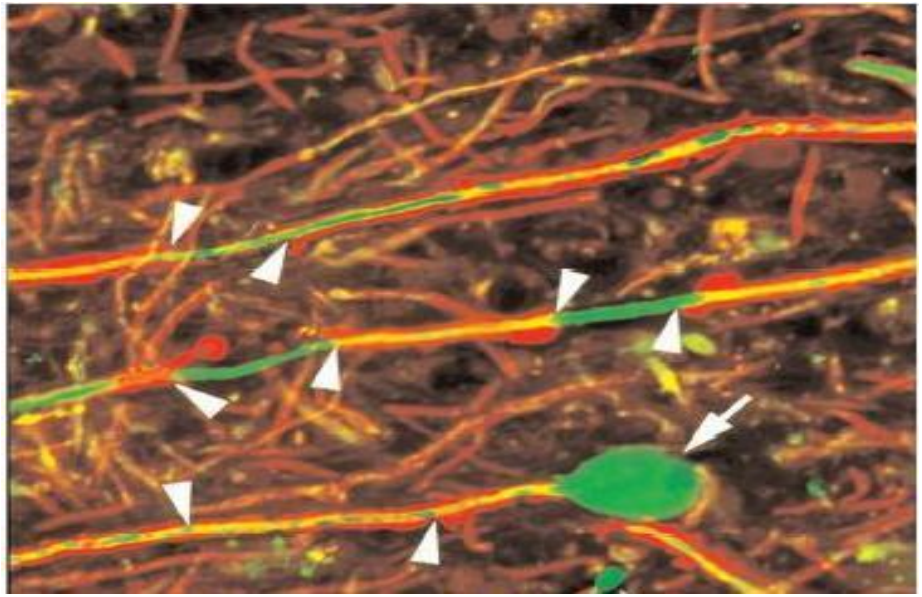
Επιστημονική Ημερίδα
Σάββατο, 25 Μαΐου 2024, ώρα 10.00 π.μ.
Ξενοδοχείο Mediterranean, Λεμεσός

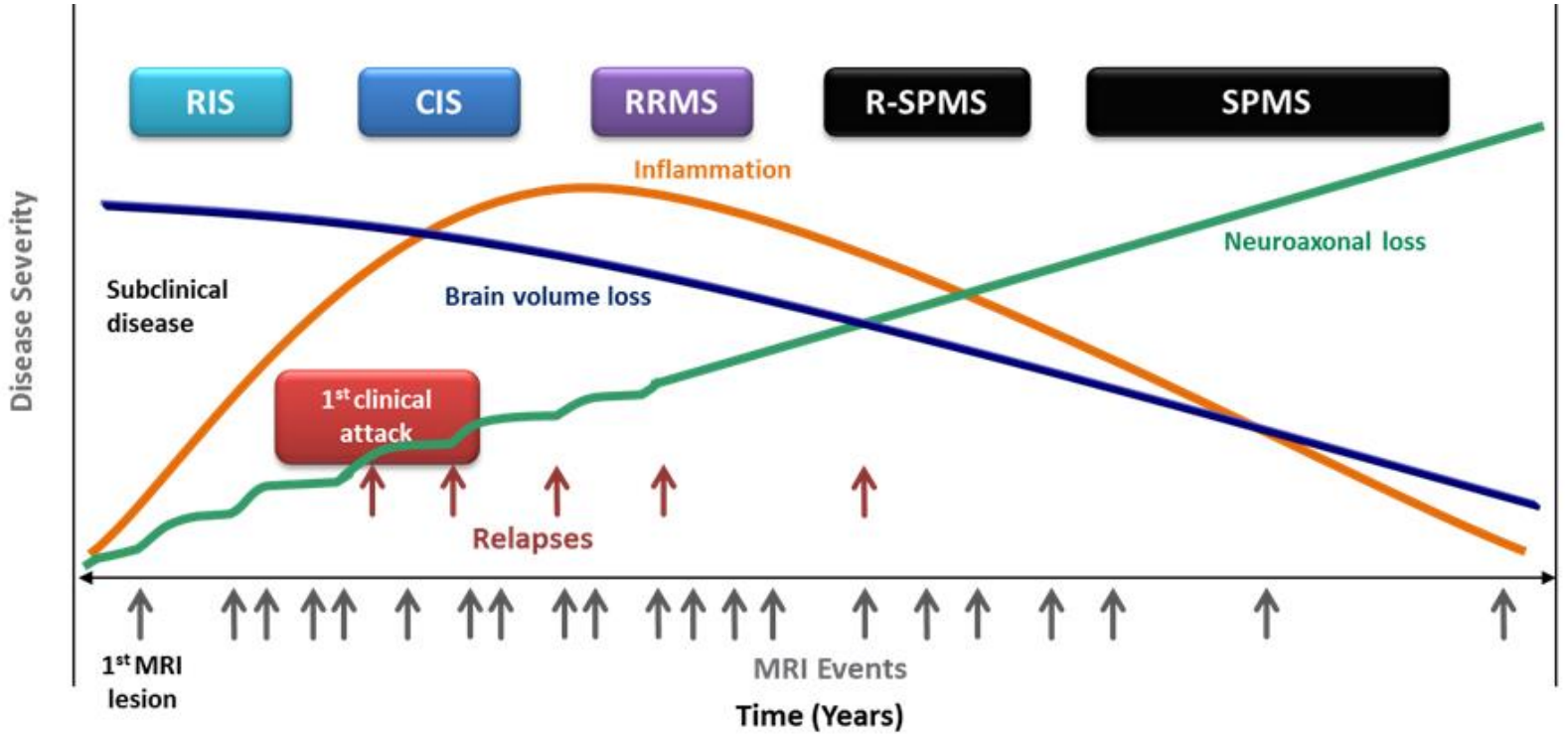
ΝΕΩΤΕΡΑ ΔΕΔΟΜΕΝΑ ΣΤΗΝ ΠΟΛΛΑΠΛΗ ΣΚΛΗΡΥΝΣΗ

Marios Pantzaris, MD, Consultant Neurologist,
Professor, CING Postgraduate School,
Department of Neuroimmunology, Head
The Cyprus Institute of Neurology and Genetics

Multiple Sclerosis- Chronic Neurodegenerative Disease







- Multiple Sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the Central Nervous System (CNS) affecting both the Brain and the Spinal Cord.

ΓΕΝΕΤΙΚΟΙ ΚΑΙ ΠΕΡΙΒΑΛΛΟΝΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ

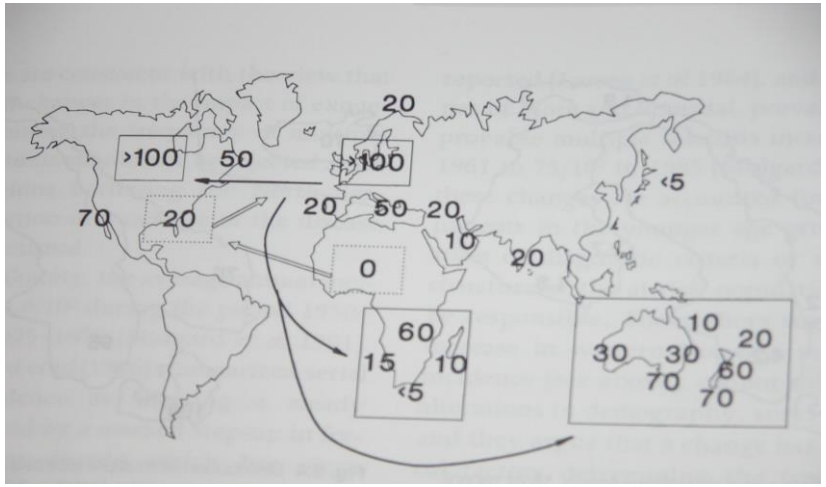
Hypothesis of the origin of Multiple Sclerosis

•Probable origin from South Scandinavia (12th century AC).

•Vikings with their fleet travelled a lot through sea transferring genes and other environmental(?) factors to all areas they invaded.

•Major destination and invasion: the British Islands and from there to their colonies.

•For many years they mastered and dominate in all known seas and participated in Byzantine army. They even took part in crusades.



New research with ancient human DNA shows the origins of MS risk genes

An international collaboration of researchers has shown genes linked to MS may have evolved as a way to protect against infections.

There's no single gene that will definitely cause someone to develop MS. But having certain versions of particular genes can increase the risk. So far we've discovered over 200 genes that are linked to MS.

New research has looked at the origins of some of these genes using ancient human DNA. They found these genes were introduced to Europe around 5,000 years ago.

RESEARCH ARTICLE SUMMARY

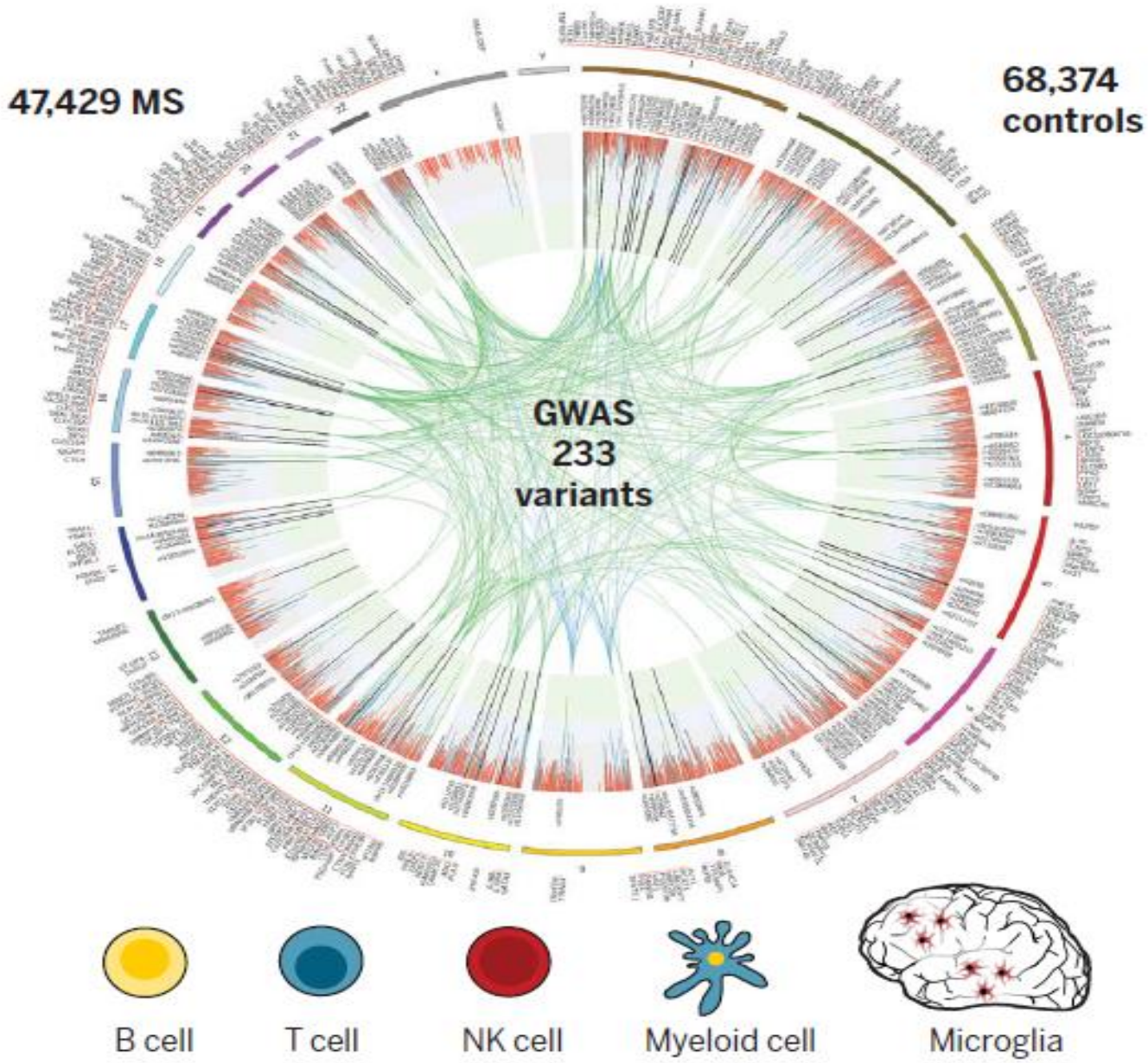
HUMAN GENOMICS

Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility

International Multiple Sclerosis Genetics Consortium*†

Patsopoulos NA, Baranzini SE, Santaniello A, Shoostari P, Cotsapas C, Wong G, et al. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science (2019) 365:eaav7188. doi: 10.1126/science.aav7188

We identified **233 statistically independent associations** with MS susceptibility that are genome-wide significant. The major histocompatibility complex (MHC) contains 32 of these associations, and one, the first MS locus on a sex chromosome, is found in chromosome X. The remaining 200 associations are found in the autosomal non-MHC genome.



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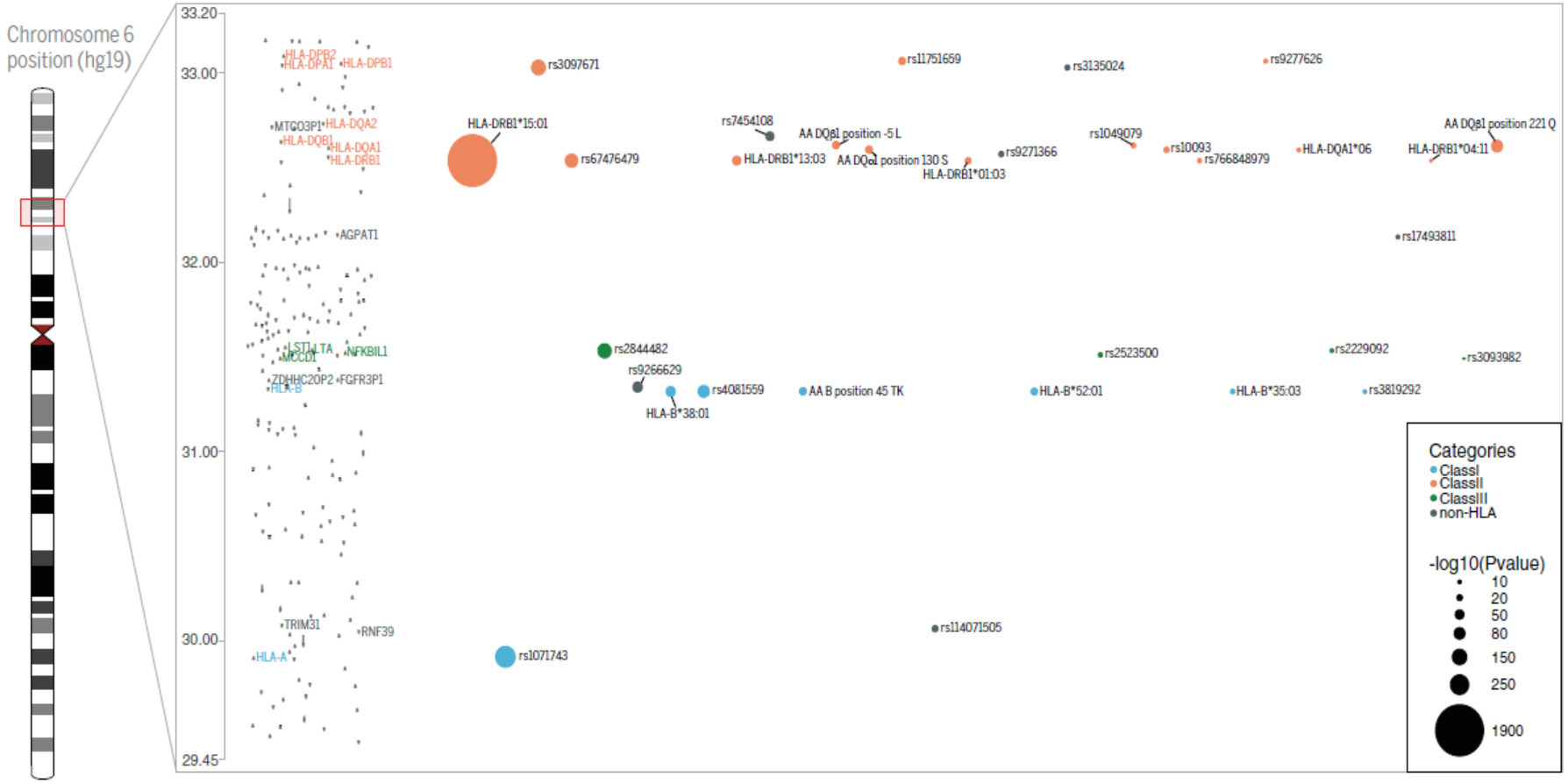

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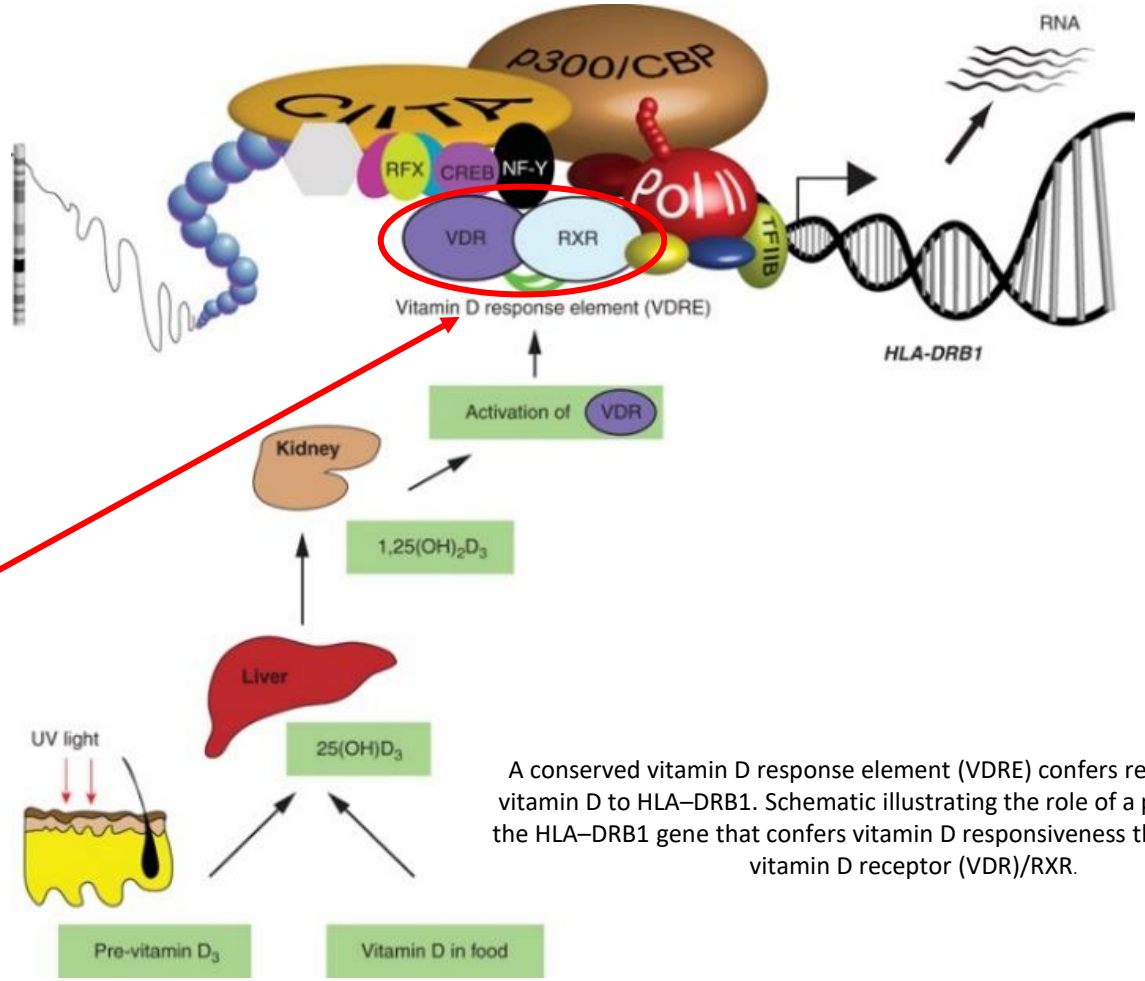
VIEWS & REVIEWS

Multiple sclerosis, vitamin D, and *HLA-DRB1*15*

Neurology® 2010;74:1905-1910

Experiments provide evidence for a direct biological interaction between HLA-DRB1, the main MS susceptibility locus, and vitamin D, a key candidate for mediating the environmental effect. The role of this interaction in disease etiology remains to be discovered but **it is plausible that a lack of vitamin D in early childhood can affect the expression of HLADRB1 in the thymus**. It can be speculated that **a general reduction in the expression of disease-associated class II alleles including HLA-DRB1*15 in the thymus during early life might result in loss of central tolerance, perhaps increasing the risk of autoimmunity in later life**.



A conserved vitamin D response element (VDRE) confers responsiveness to vitamin D to HLA–DRB1. Schematic illustrating the role of a proximal VDRE at the HLA–DRB1 gene that confers vitamin D responsiveness through binding of vitamin D receptor (VDR)/RXR.

Genes and Immunity (2010) 11, 99–112

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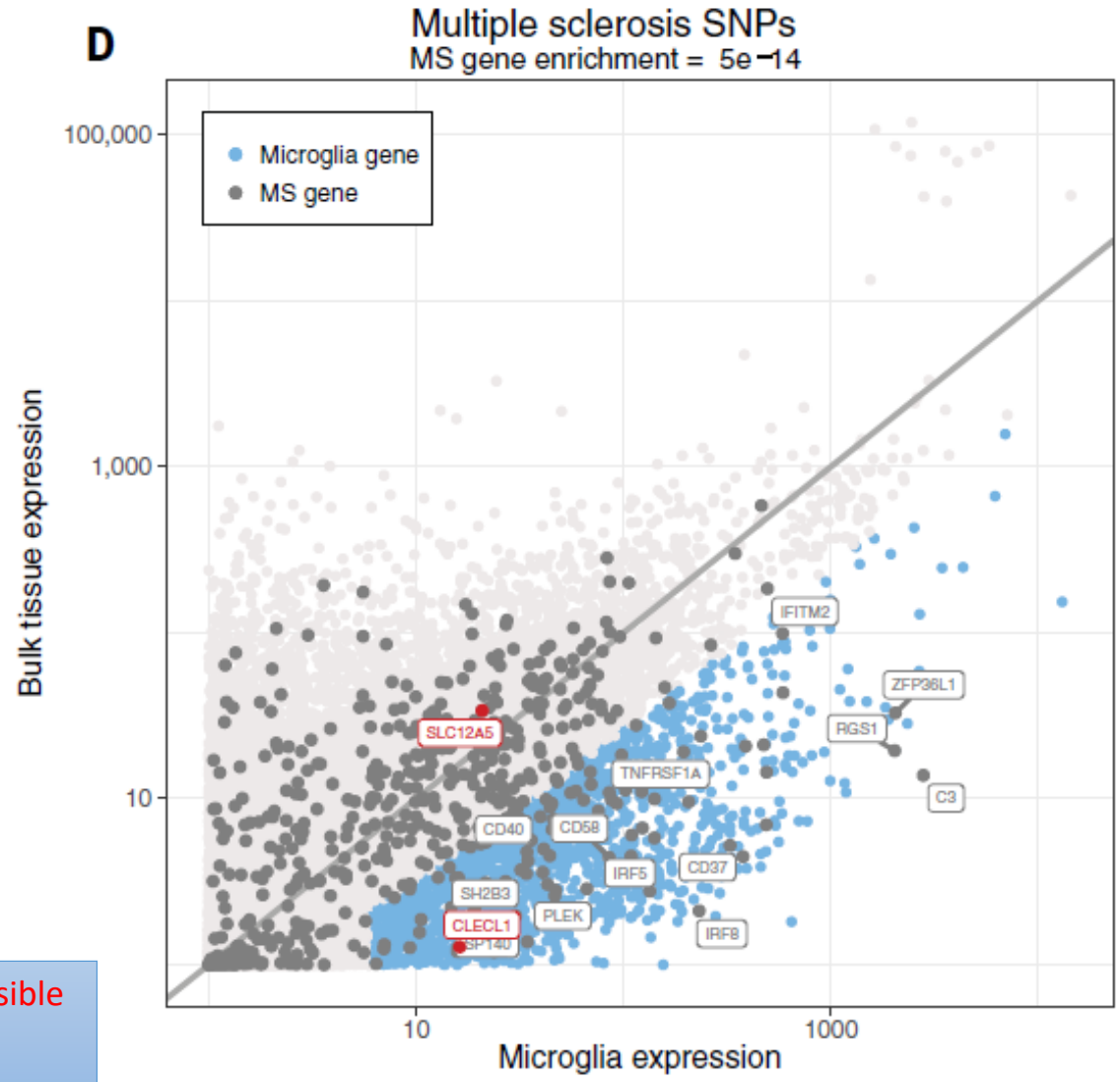
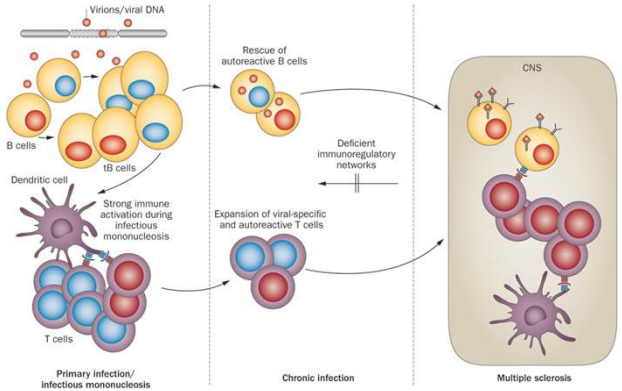


the myeloid component highlights a possible role for microglia that requires further investigation and the B cell component

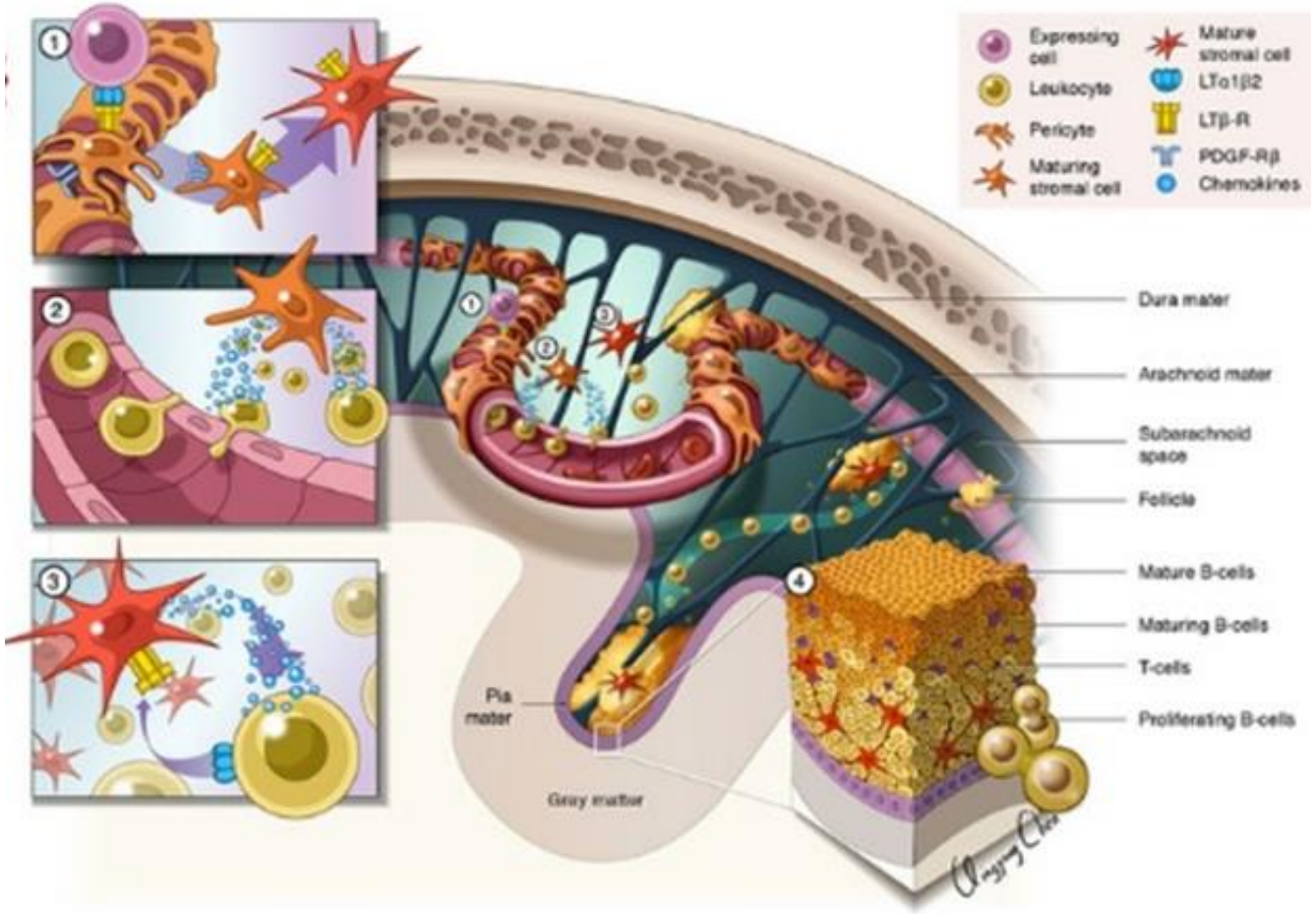
EBNA1-specific T cells from patients with multiple sclerosis cross react with myelin antigens and co-produce IFN-γ and IL-2

EBV VIRUS AND MULTIPLE SCLEROSIS

J. Exp. Med. Vol. 205 No. 8 1763-1773
www.jem.org/cgi/doi/10.1084/jem.20072397



Compared with healthy individuals, patients with MS show higher frequencies and activation states of self-reactive B lymphocytes (cells with red nuclei), in addition to impaired functions of regulatory immune compartments, indicating a lower threshold for **breakdown of self-tolerance to CNS antigens**. Strong innate immune activation during primary EBV infection could facilitate activation and expansion of autoreactive and polyspecific (that is, both autoantigen-specific and viral-antigen-specific [cells with blue nuclei]) T and B cells. These cells could be maintained in the presence of continuous antigen exposure. In addition, latent EBV infection confers B-cell **(anti-EBNA-1-producing plasma cells)** survival advantages and could rescue autoreactive B cells from apoptotic deletion during B-cell development and differentiation. Homing of these rescued autoreactive lymphocytes, which can immuno-modulate and present antigen to T cells, to the inflamed CNS might contribute to the immunopathology of MS.



Nature Reviews Neurology 8, 602-612 (November 2012)

Bjornevik *et al.*, *Science* **375**, 296–301 (2022)

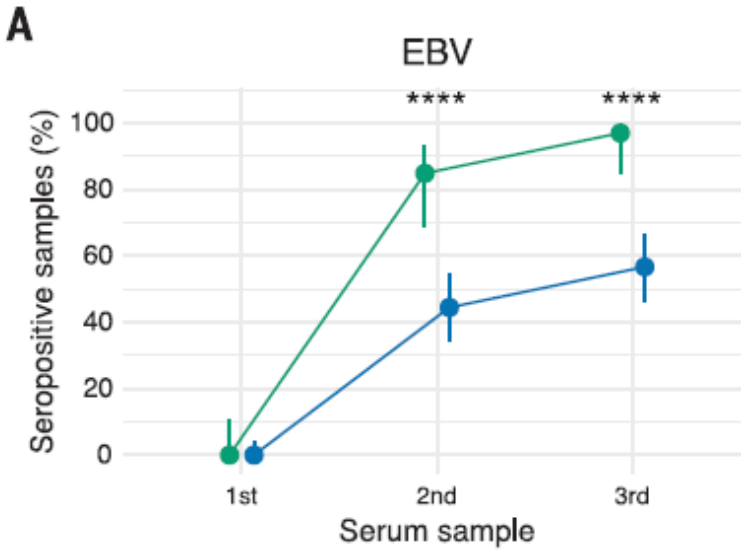
REPORT

MULTIPLE SCLEROSIS

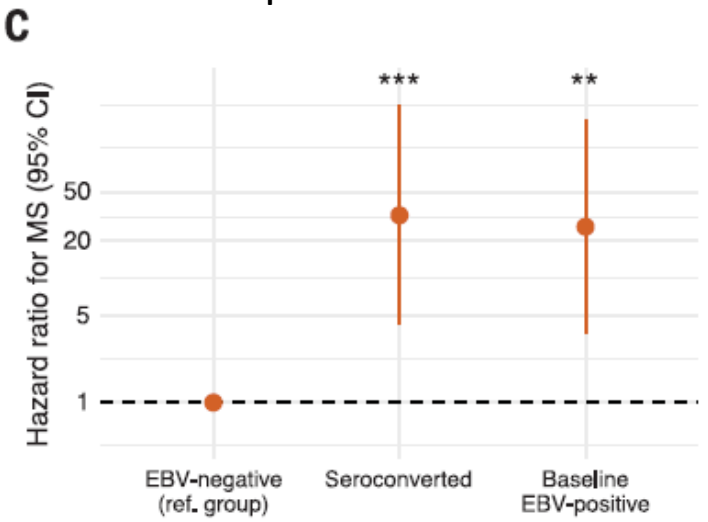
Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

- We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, over the course of a 20-years, between 1993 and 2013.
- We identified 955 of whom were diagnosed with MS during their period of service.
- There were 801 MS cases and 1566 controls with samples available to assess EBV infection status (at least 3 samples)



EBV negative at baseline and with EBV measurement in three samples. A significantly higher proportion of individuals who later developed MS were EBV positive in the second and third samples compared with individuals who did not develop MS



The risk ratio for MS according to EBV status. EBV seroconversion by the time of the third sample and EBV seropositivity at the time of the first sample were associated with a 32-fold and 26-fold increased risk of developing MS, respectively

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 24 July 2023
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OPEN ACCESS

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Risk factors for multiple sclerosis in the context of Epstein-Barr virus infection

Anna Karin Hedström*

Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

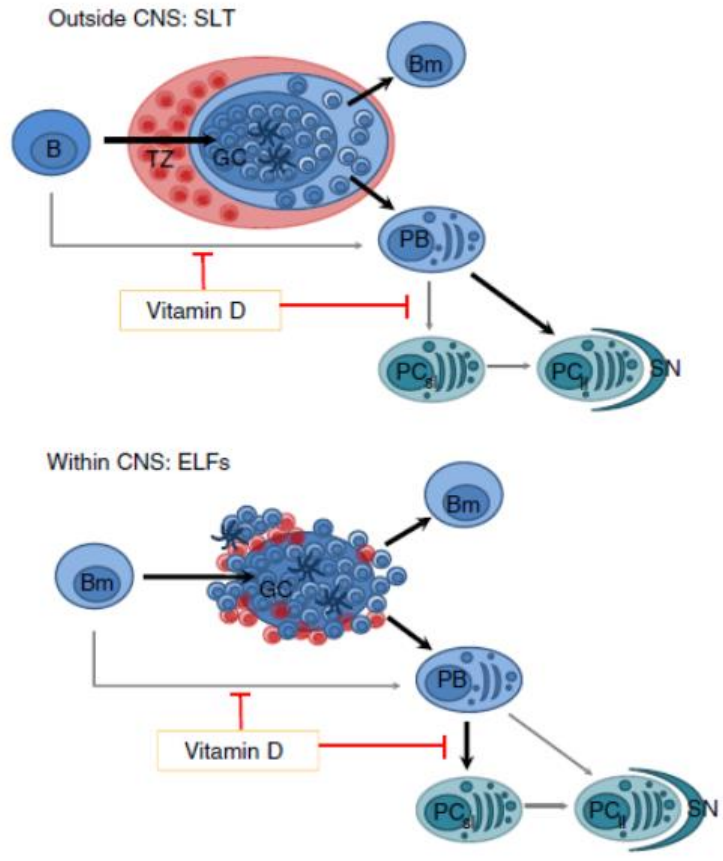
Risk factors	OR for each risk factor in the absence of the other/s	Combined OR
Anti-EBNA 50-75th percentile* Adolescent BMI>25 kg/m^2	2.1 + 1.5	2.7
Anti-EBNA 75-95th percentile* Adolescent BMI>25 kg/m2	3.4 + 1.4	4.6
Anti-EBNA >95th percentile * Adolescent BMI>25 kg/m2	4.0 + 1.4	7.3
Anti-EBNA>median HLA-DRB1*15:01 positive Adolescent BMI>25 kg/m2	2.5 + 2.8 + 1.6	13.5
Past IM Adolescent BMI>27 kg/m2	1.8 + 1.7	8.1
Past IM Adolescent BMI>27 kg/m2	1.8 + 1.6	7.0
Past IM DRB1*1501 positive Adolescent BMI>25 kg/m2	2.0 + 3.4 + 1.4	22.2

Risk factors	OR for each risk factor in the absence of the other/s	Combined OR
High anti-EBNA Ever smoking	1.8 + 2.5	2.7
Anti-EBNA>median Ever smoking	2.7 + 1.5	3.8
Anti-EBNA>median Current smoking	2.7 + 1.6	4.4
Anti-EBNA>75th percentile Ever smoking	4.1 + 0.6	7.4
Past IM Ever smoking	1.5 + 2.1	3.2
Past IM Current smoking	1.8 + 1.6	3.0

Risk factors for MS onset in the context of EBV

- Viral infections apart from EBV
- Genetics
- Sun exposure and vitamin D
- Lung-irritating agents
- Obesity
- Other potential risk factors (microbiome and PUFAs)

VITAMIN D AND B-LYMPHOCYTES*



*anti-EBNA-1-producing plasma cells

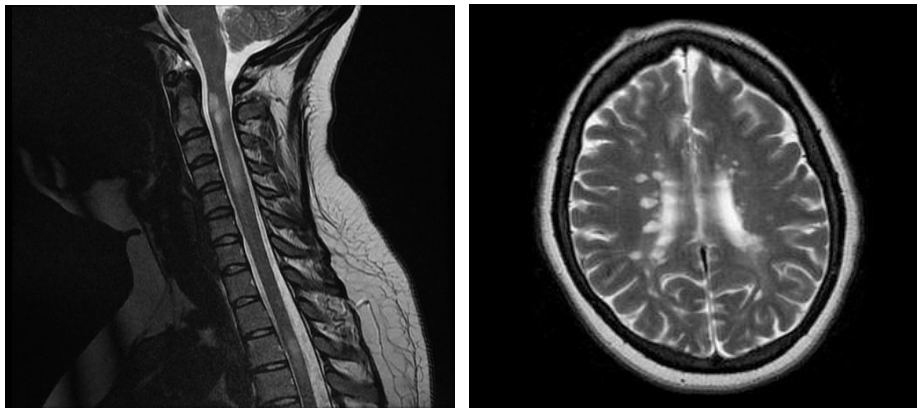
In vivo plasma cell generation **outside the central nervous system** may occur outside or (in most cases) within lymph secondary lymphoid tissue/GCs. In case GC processes (class switch recombination/somatic hypermutation) are involved, plasma blasts may be generated with a selection advantage for becoming long-lived plasma cells. Those reside in survival niches, enabling ongoing immunoglobulin production (stable immunoglobulin levels).
In vivo plasma cell generation **within the central nervous system** probably takes place in ectopic lymphoid follicles. Here functionally inferior GCs compared with the ones of secondary lymphoid tissue, generate plasma blasts without the selection advantage for becoming long-lived plasma cells.

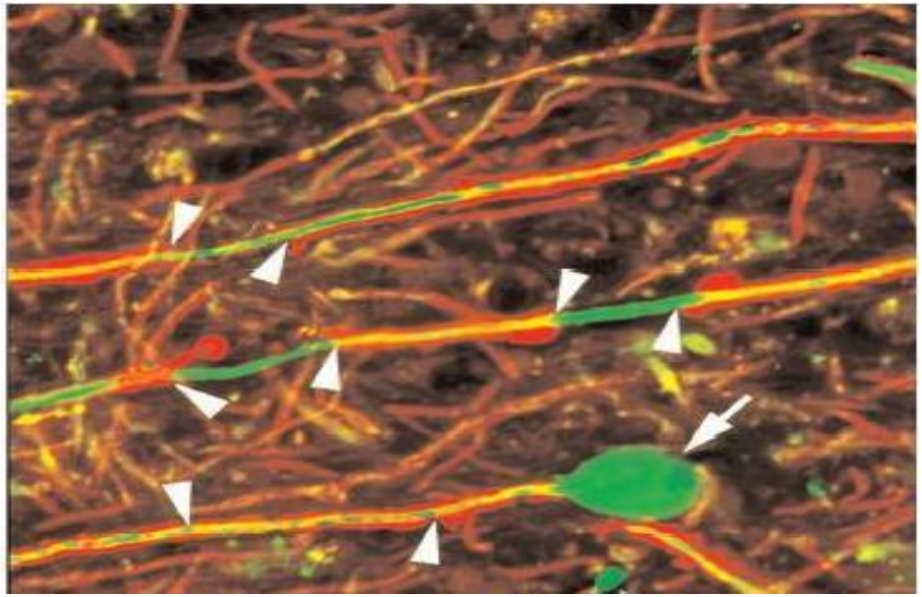
Abbreviations: B, B cell (naive/ memory); PB, plasma blast; PC, plasma cell; CNS, central nervous system; SLT, secondary lymphoid tissue; TZ, T-cell zone; GC, germinal centre; Bm, memory B cell; PCsl, short-lived plasma cell; PCll, long-lived plasma cell; SN, survival niche; ELFs, ectopic lymphoid follicles

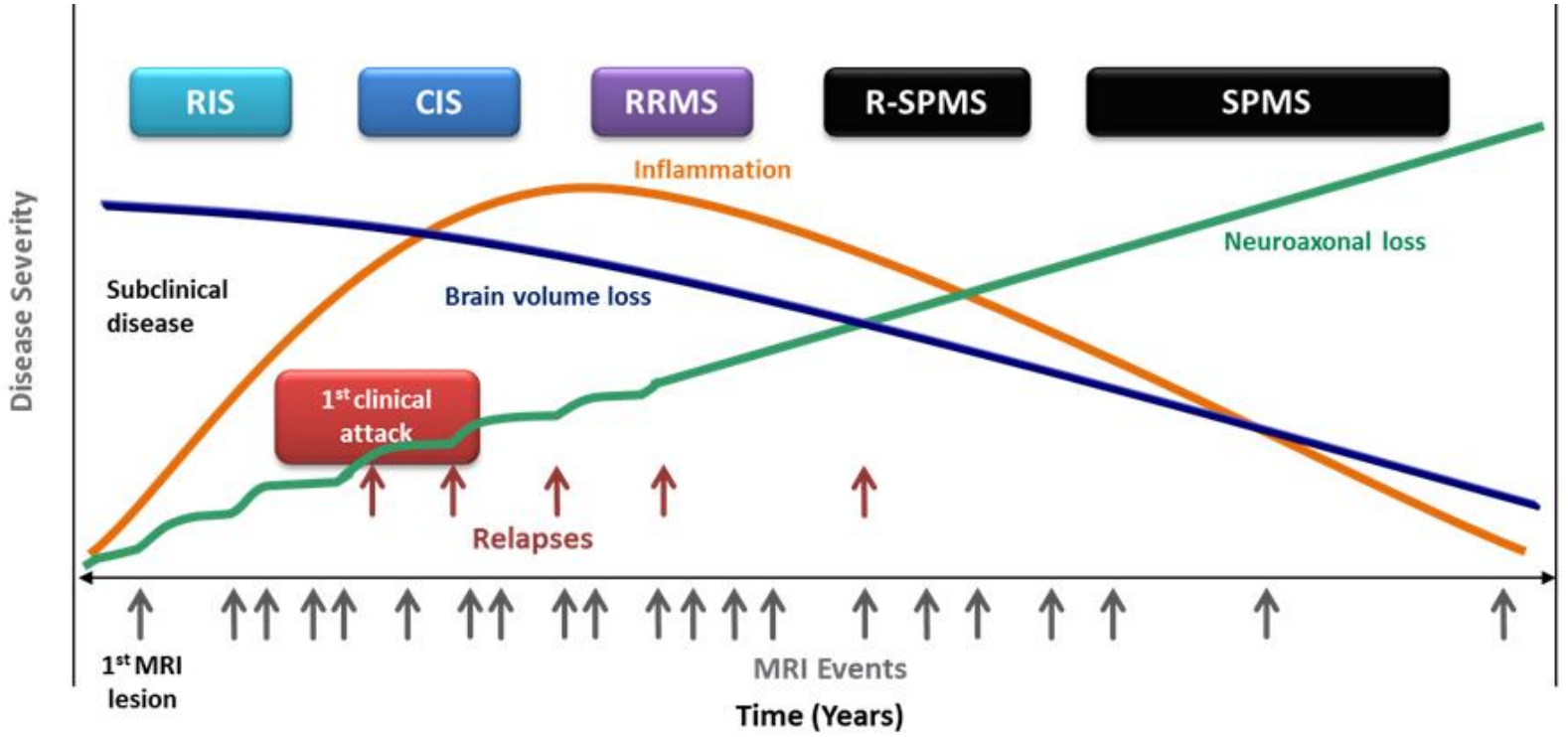
Immunology 2015; 147: 275–284

Η ΦΛΕΓΜΟΝΗ

Multiple Sclerosis- Chronic Neurodegenerative Disease







- Multiple Sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the Central Nervous System (CNS) affecting both the Brain and the Spinal Cord.

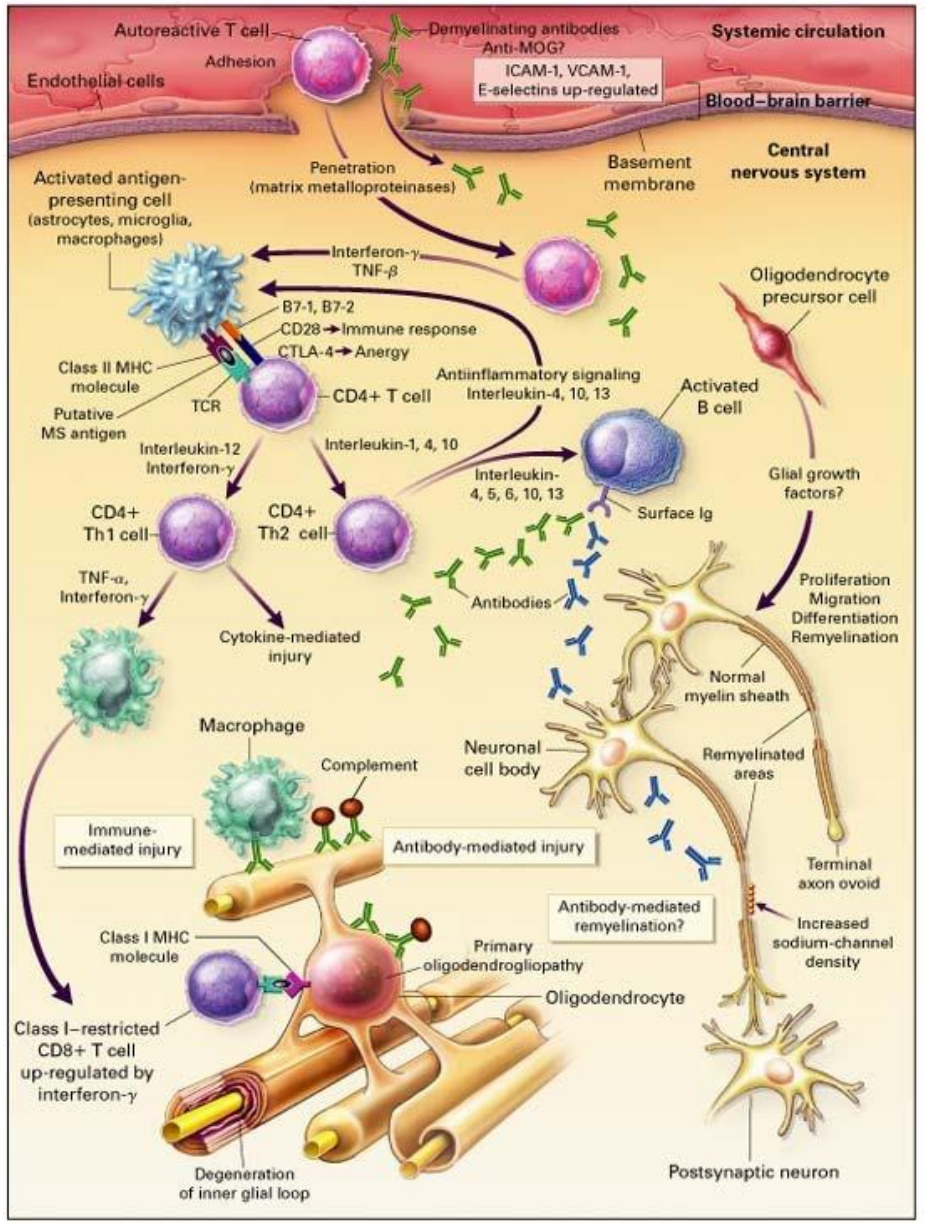
There are two different types of inflammation in MS patients:

The first pattern, which is associated with:

the focal bulk invasion of inflammatory cells into the brain and

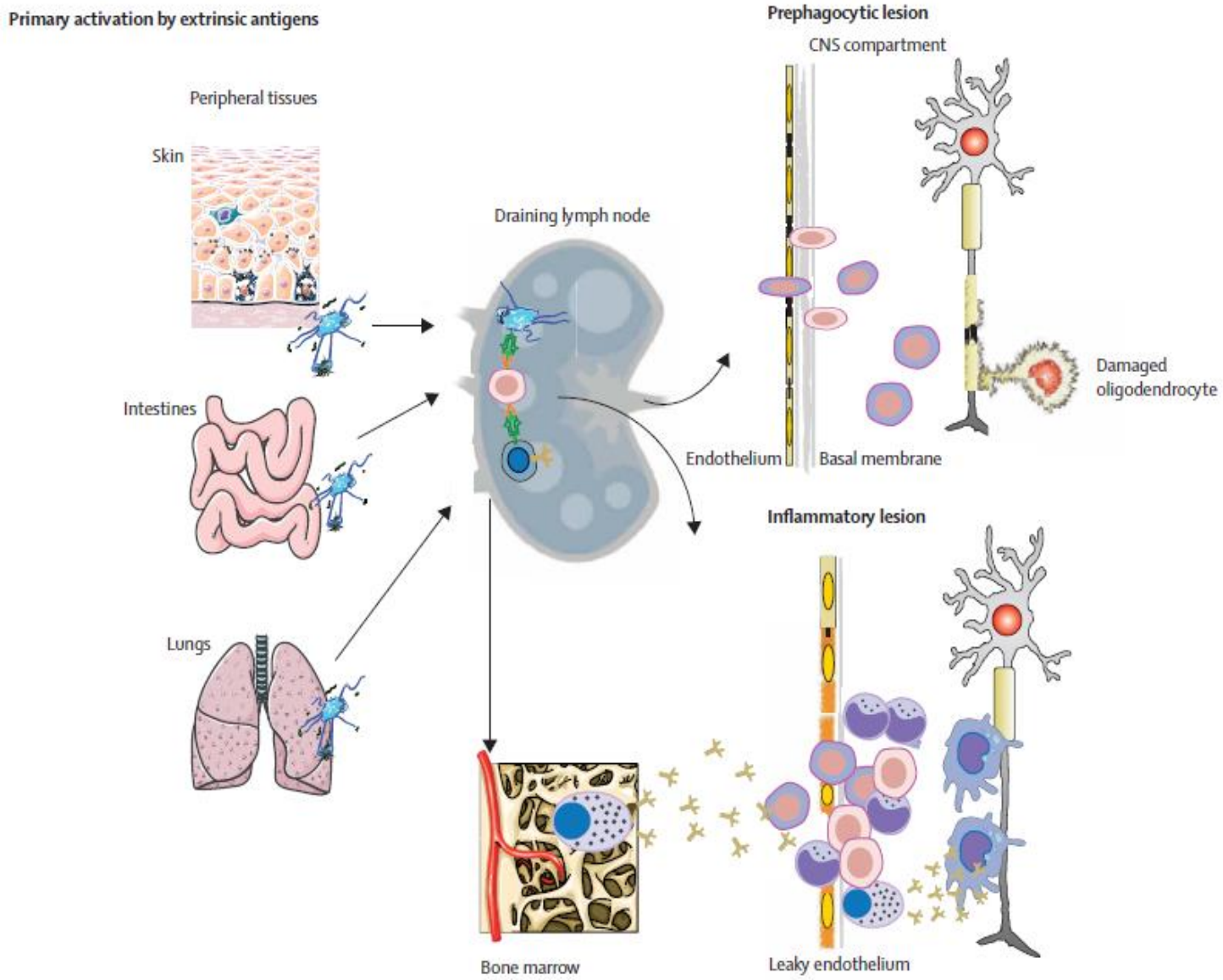
the formation of new focal lesions mainly in the white matter.

- Due to a major disturbance of the blood-brain barrier.
- With lymphocytes entering the brain in the course of immune surveillance,
- Lymphocyte recognition of their cognate-antigen within the central nervous system,
- Re-activation of these lymphocytes,
- Production of a variety of pro-inflammatory mediators, activation of microglia and
- Recruitment of additional cells and *serum components* through the *impaired blood-brain barrier*.



Role of the innate and adaptive immune responses in the course of multiple sclerosis

Review Bernhard Hemmer, Martin Kerschensteiner, Thomas Korn *Lancet Neurol* 2015; 14: 406–19



Outside-in Model

A **major hypothesis** in multiple sclerosis pathology is that a CNS antigen-specific immune activation occurs first in **the periphery** and is then transferred to the previously unaffected CNS.
After migration to the lymph nodes, a few of these antigen-specific T cells and B cells will invade the CNS compartment during the pre-phagocytic phase of lesion development.
The release of inflammatory mediators will open the blood–brain barrier and attract the influx of monocytes and additional lymphocytes and other ***serum components***, leading to the formation of the phagocytic lesion.

Role of the innate and adaptive immune responses in the course of multiple sclerosis

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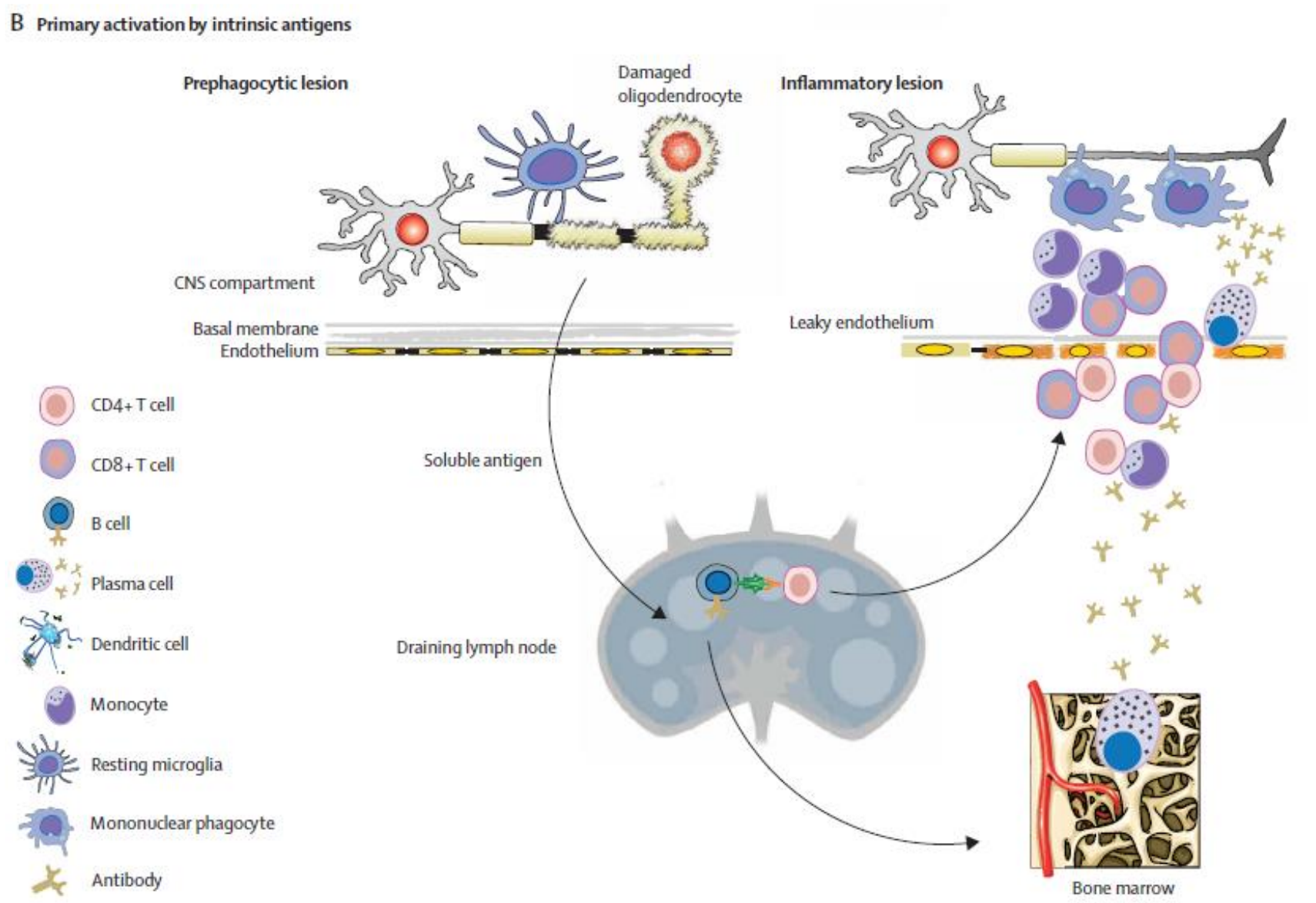


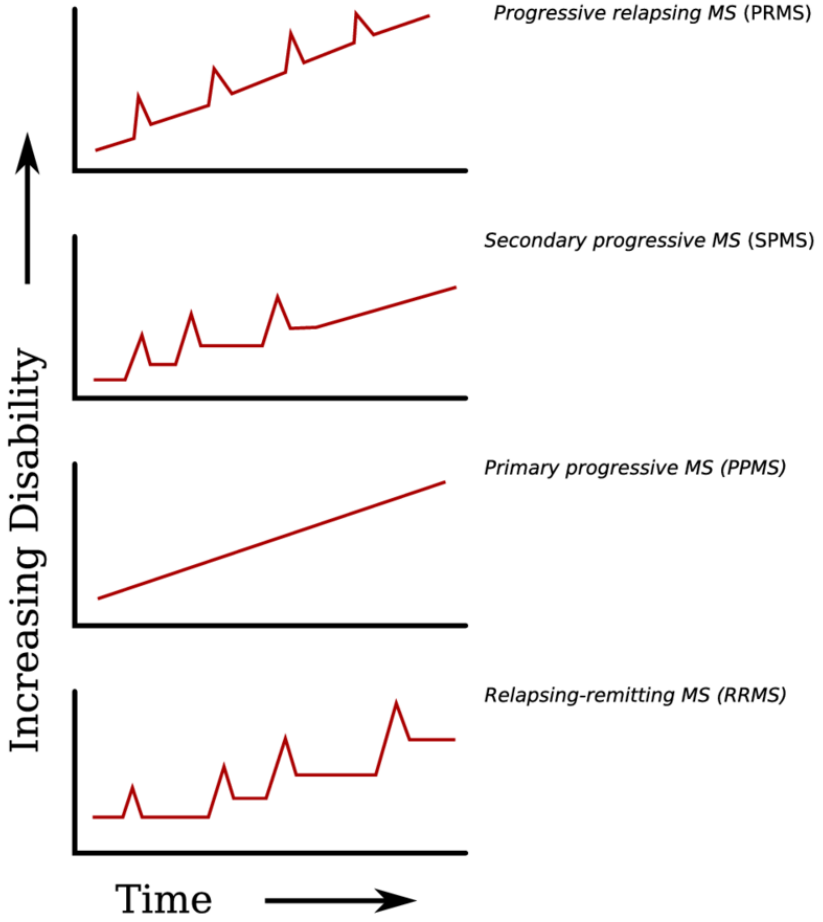
Inside-out Model

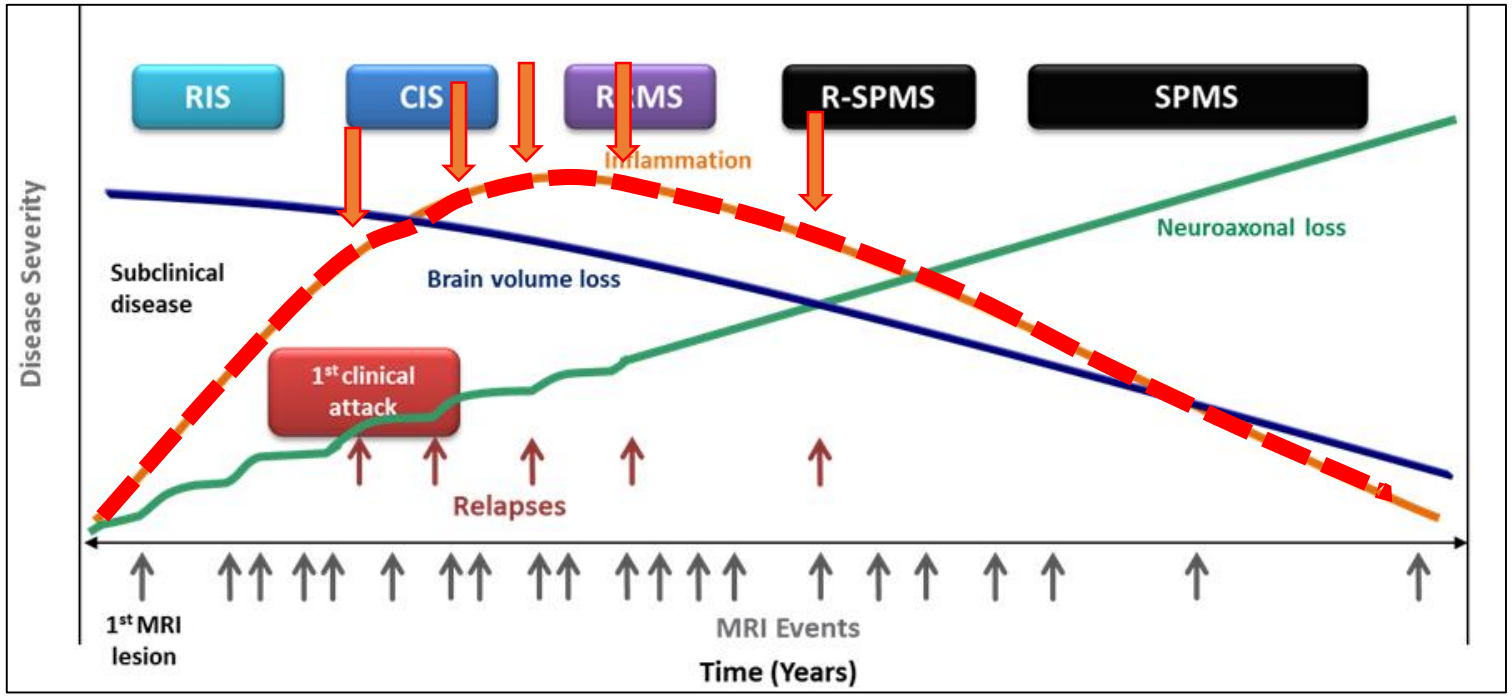
In an **alternative hypothesis,** an initiating event within the CNS causes the subsequent activation of resident microglia and an amplification of the immune reaction, with a secondary recruitment of adaptive and innate immune cells.

In this hypothesis, a primary defect of oligodendrocytes (eg, a genetic mutation/ viral/ toxic agent) leads to spontaneous oligodendrocyte death and consecutive activation of microglial cells, which would account for the changes noted in pre-phagocytic lesions

In this proposed hypothesis, antigens drain out of the CNS into deep cervical lymph nodes to induce a secondary adaptive immune response in the periphery.

Multiple Sclerosis- First Pattern of Inflammation

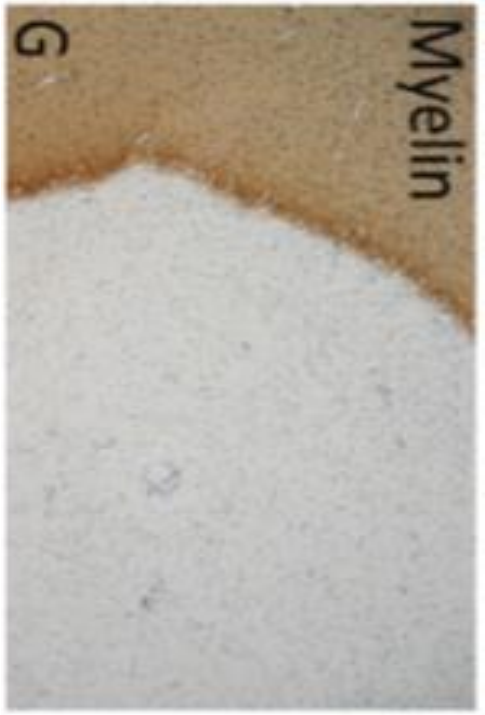




There are two different types of inflammation in MS patients:

- **The second pattern** of inflammation in the MS brain is an inflammatory reaction, which accumulates in the large connective tissue spaces of the brain and spinal cord, dominantly *affecting the meninges and the large periventricular Virchow Robin spaces*. B-cell lineage, CD20 positive cells are most frequent in active lesions, but *the majority of cells present in chronic lesions are plasma blasts and plasma cells*. In the meninges and perivascular space this *inflammatory reaction is present diffusely but it may form focal aggregates* or structures, which resemble tertiary **lymph follicles** with clearly separated T-cell, B-cell, and plasma cell areas.

- In contrast to the inflammatory reaction in classical active white matter lesions *blood-brain barrier damage is minor or absent in this compartmentalized inflammatory reaction* ***in chronic progressive MS***. The *meningeal and perivascular infiltrates are associated with slow expansion to the white and gray matter*. Tissue injury may at least be partly mediated by a cascade *involving microglia and macrophage activation, oxidative injury, and mitochondrial damage*. Soluble factors, produced by the inflammatory cells, may exert tissue damage either directly or indirectly by the activation of microglia or macrophage and also astrocytes.

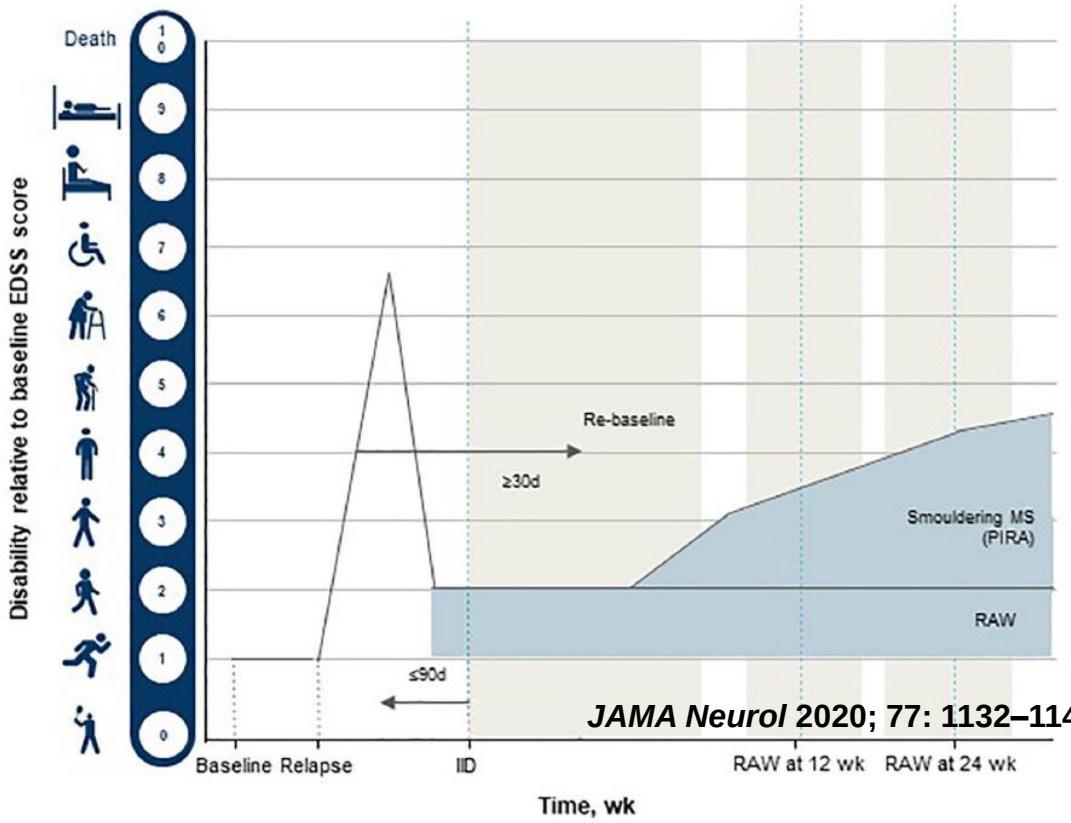


Therapeutic Advances in Neurological Disorders
2022, Vol. 15: 1–18
DOI: 10.1177/
17562864211066751

Smouldering multiple sclerosis: the 'real MS'

Gavin Giovannoni, Veronica Popescu, Jens Wuerfel, Kerstin Hellwig, Ellen Iacobaeus, Michael B. Jensen, José Manuel García-Domínguez, Livia Sousa, Nicola De Rossi, Raymond Hupperts, Giuseppe Fenu, Benedetta Bodini, Hanna-Maija Kuusisto, Bruno Stankoff, Jan Lycke, Laura Airas, Cristina Granziera and Antonio Scalfari

A large proportion of people with multiple sclerosis (MS) continue to experience clinical deterioration despite a lack of overt ongoing inflammatory disease activity. To this end, such patients exhibit disability progression despite being relapse-free and exhibiting neither contrast-enhancing T1-weighted (T1w) lesions nor new or enlarging T2-weighted (T2w) lesions on magnetic resonance imaging (MRI). This is often referred to as progression independent of relapse activity (PIRA) or smouldering MS.



JAMA Neurol 2020; 77: 1132–114

In relapsing-remitting MS (RRMS), the effective therapeutic suppression of relapses does not always correlate with the prevention of long-term disability accumulation, thus highlighting a disconnect between mechanisms underlying **inflammatory attacks** and those responsible for **disease progression**.

frontiers in Immunology

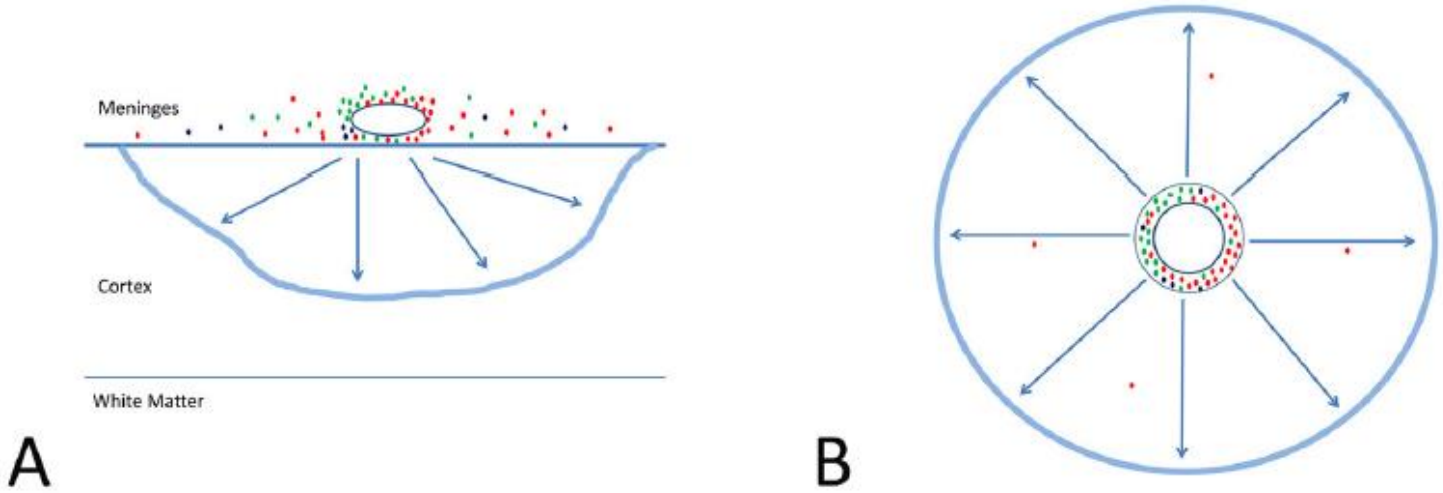
REVIEW
published: 10 January 2019
doi: 10.3389/fimmu.2018.03116

Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis

Slowly expanding lesions in progression of MS in the cortex and the white matter.

*Hans Lassmann**

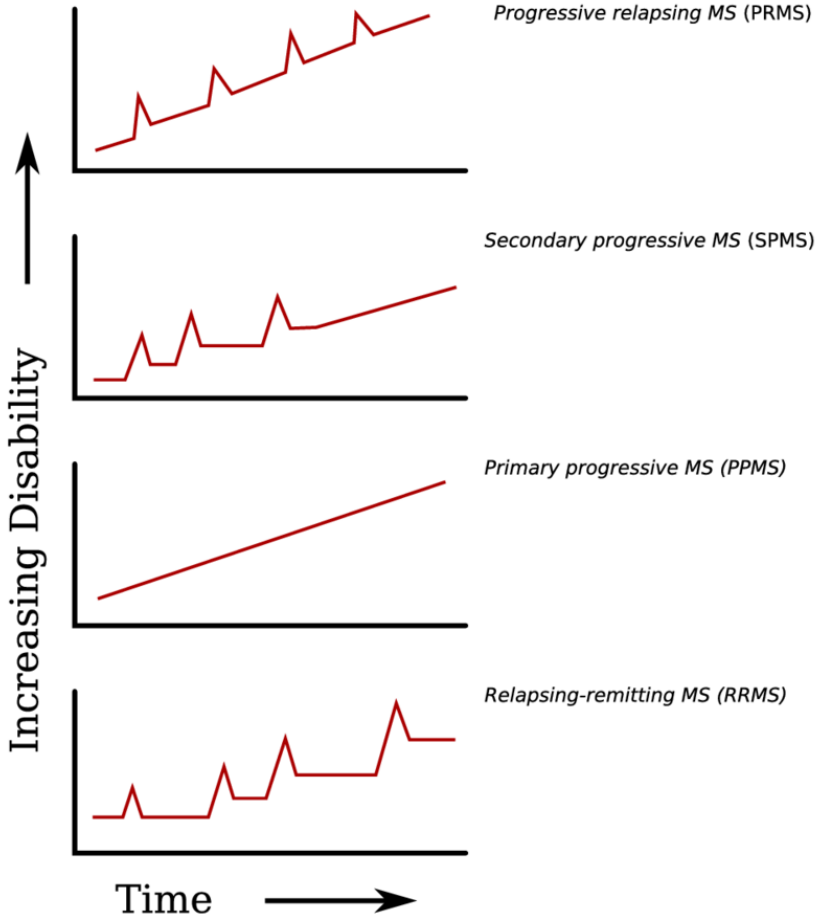
Center for Brain Research, Medical University of Vienna, Vienna, Austria

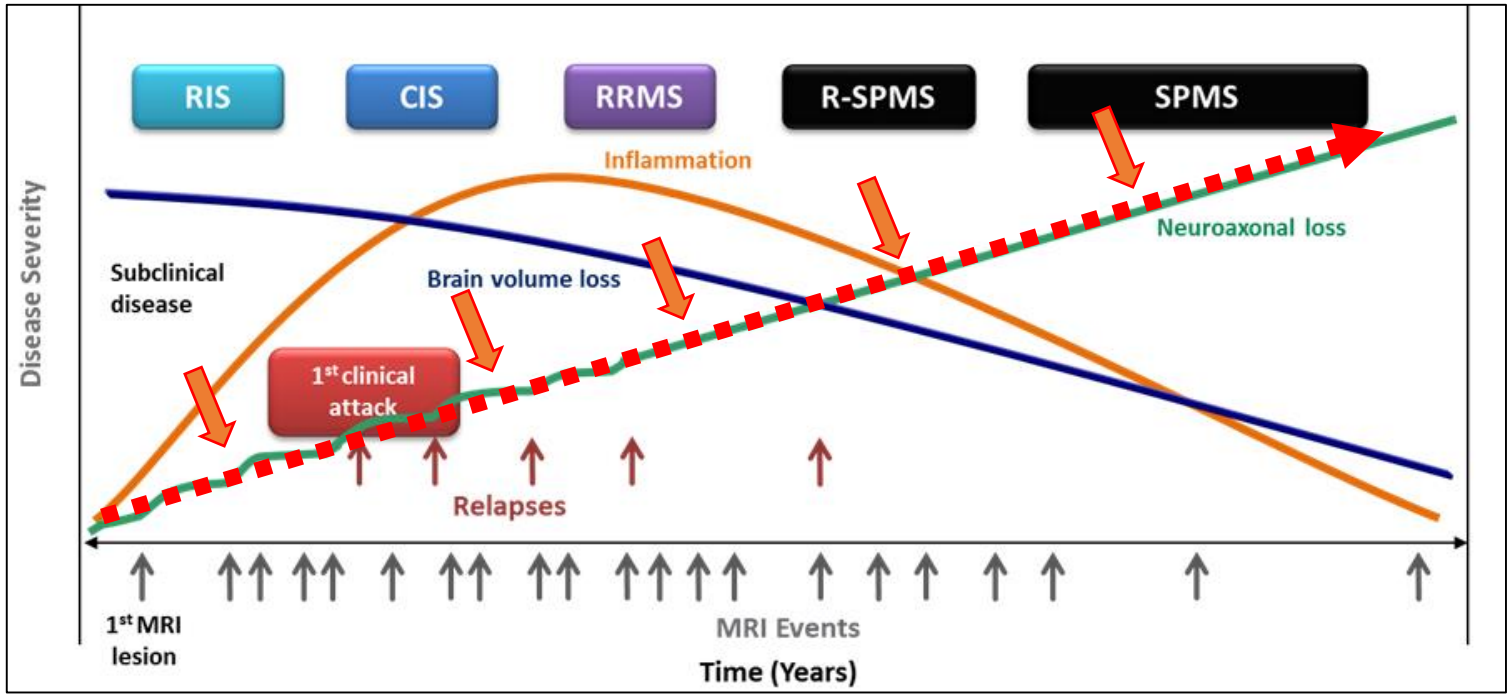


(A) ***Active cortical lesions*** are associated with inflammatory infiltrates in the meninges, which are composed of CD8+ T-cells (red), CD20+ B-cells (green) and plasma cells (blue). Active demyelination occurs at a distance of the inflammatory infiltrates and is associated with activated microglia (blue lesion rim). Th**e lesions gradually expand from the pial surface of the cortex toward the depth of the gray matter**. *Lymphocyte infiltrates are rare or completely absent in the cortical tissue and in particular at the zone of active demyelination*. It is suggested that the inflammatory infiltrates in the meninges produce a soluble factor, which induces demyelination and neurodegeneration either directly or indirectly through microglia activation (arrows).

(B) In ***slowly expanding lesions in the white matter*** T-cell, B-cell and plasma cell infiltrates are present in the large perivascular Virchow Robin spaces. **Active demyelination and neurodegeneration occurs at a distance and is associated with microglia activation**. Also in these lesions it is suggested that demyelination and neurodegeneration is driven by a soluble factor, produced by the perivascular lymphocytes or plasma cells (arrows).

Multiple Sclerosis- Second Pattern of Inflammation



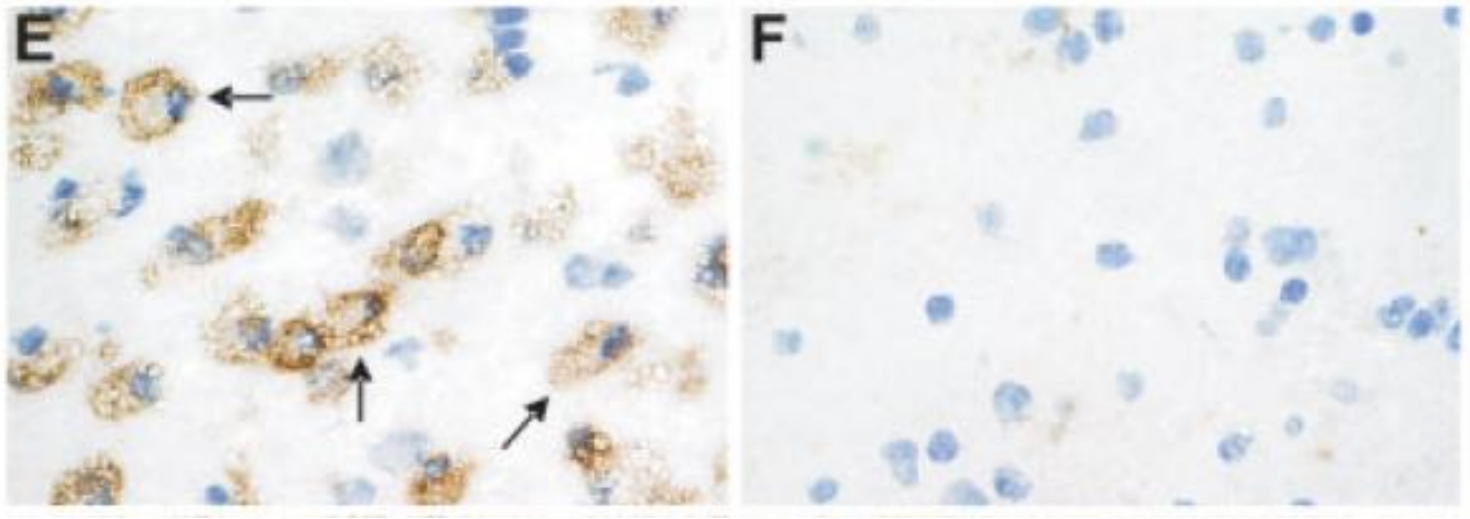


ORIGINAL ARTICLE

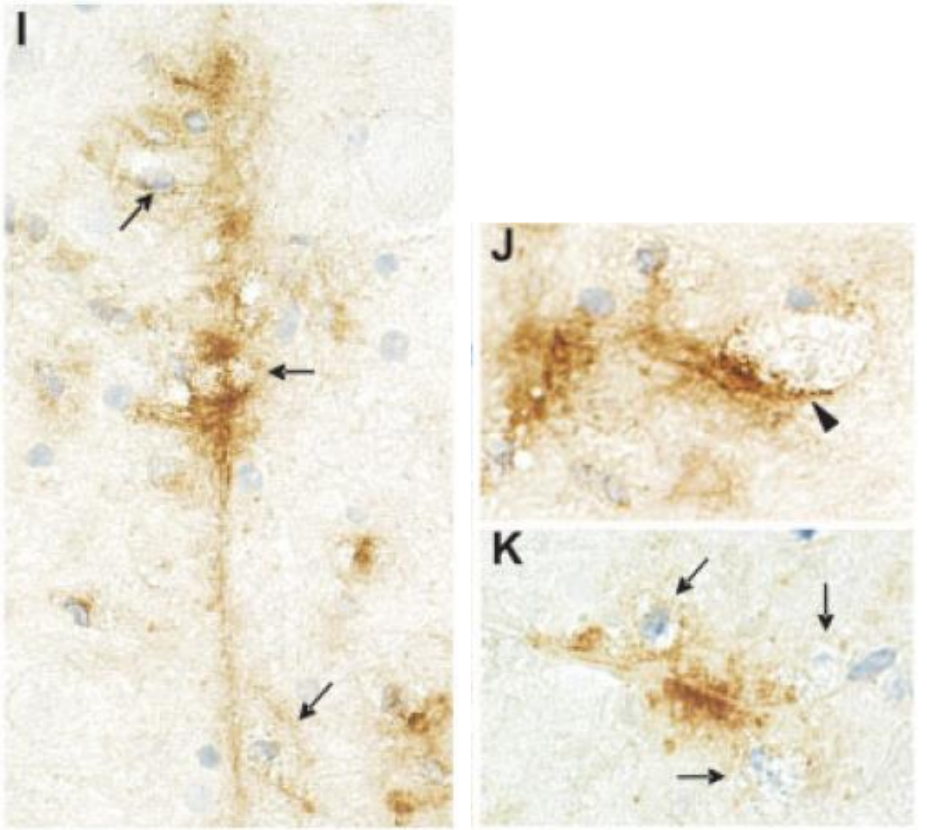
Ann Neurol 2008;63:16–25

Homogeneity of Active Demyelinating Lesions in Established Multiple Sclerosis

Esther C. W. Breij, PhD,[1] Bianca P. Brink, BSc,[2] Rob Veerhuis, PhD,[2,3] Christa van den Berg, BSc,[2] Rianka Vloet, BSc,[1] Riqiang Yan, PhD,[4] Christine D. Dijkstra, MD, PhD,[1] Paul van der Valk, MD, PhD,[2] and Lars Bö, MD, PhD[2,5]



C5b-9 immunopositivity is consistently found on and within macrophages (arrows) *in inflammatory demyelinating areas (E) but not in inflammatory non-demyelinating areas (F).*



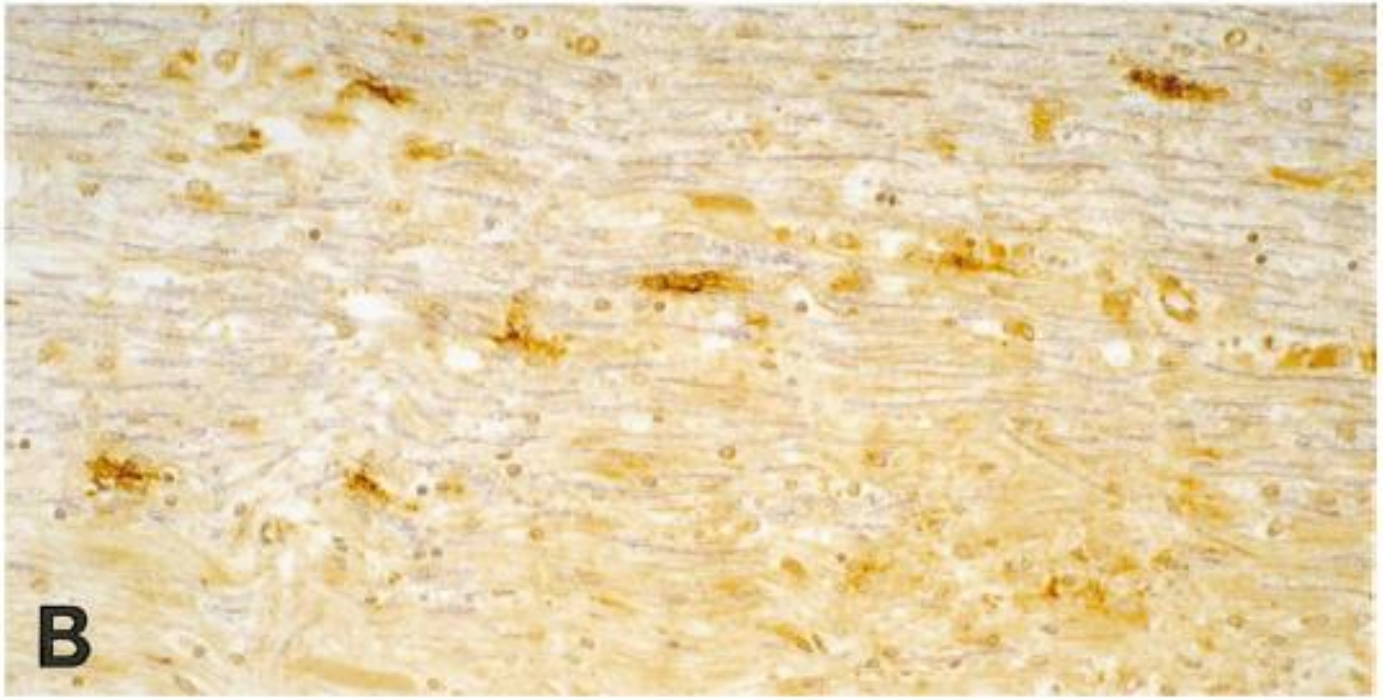
C3d immunostaining is observed on a myelin sheath that is in close contact with macrophages (arrows) *(I); immunostaining is more intense at the interface* (arrowhead) *of the myelin sheath and the macrophage (J). C4d immunostaining on a myelin sheath that is surrounded by macrophages* (arrows) *(K).*

The immunopathological appearance of active demyelinating lesions in established MS is uniform. Consistent presence of complement, antibodies, and Fc receptors in phagocytic macrophages suggests that antibody- and complement-mediated myelin phagocytosis is the dominant mechanism of demyelination in established MS.

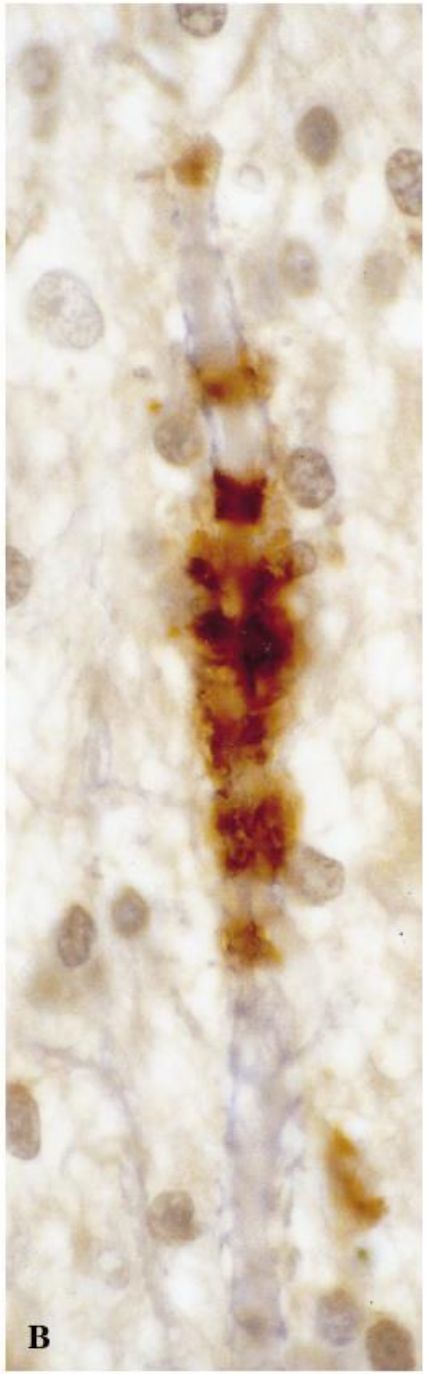
Immunopathology of Secondary-Progressive Multiple Sclerosis

Ann Neurol 2001;50:646–657

John W. Prineas, MB, BS,[1] Eunice E. Kwon, MSc,[2] Eun-Sook Cho, MD,[2] Leroy R. Sharer, MD,[2]
Michael H. Barnett, MB, BS,[1] Emilia L. Oleszak, PhD,[3] Brad Hoffman, BS,[3] and Bryan P. Morgan, PhD[4]



Edge of a lesion stained for activated complement (C3d). Scattered, short linear deposits of C3d are present in myelinated margin.



A myelin sheath located within a microglial stains positively for C3d.

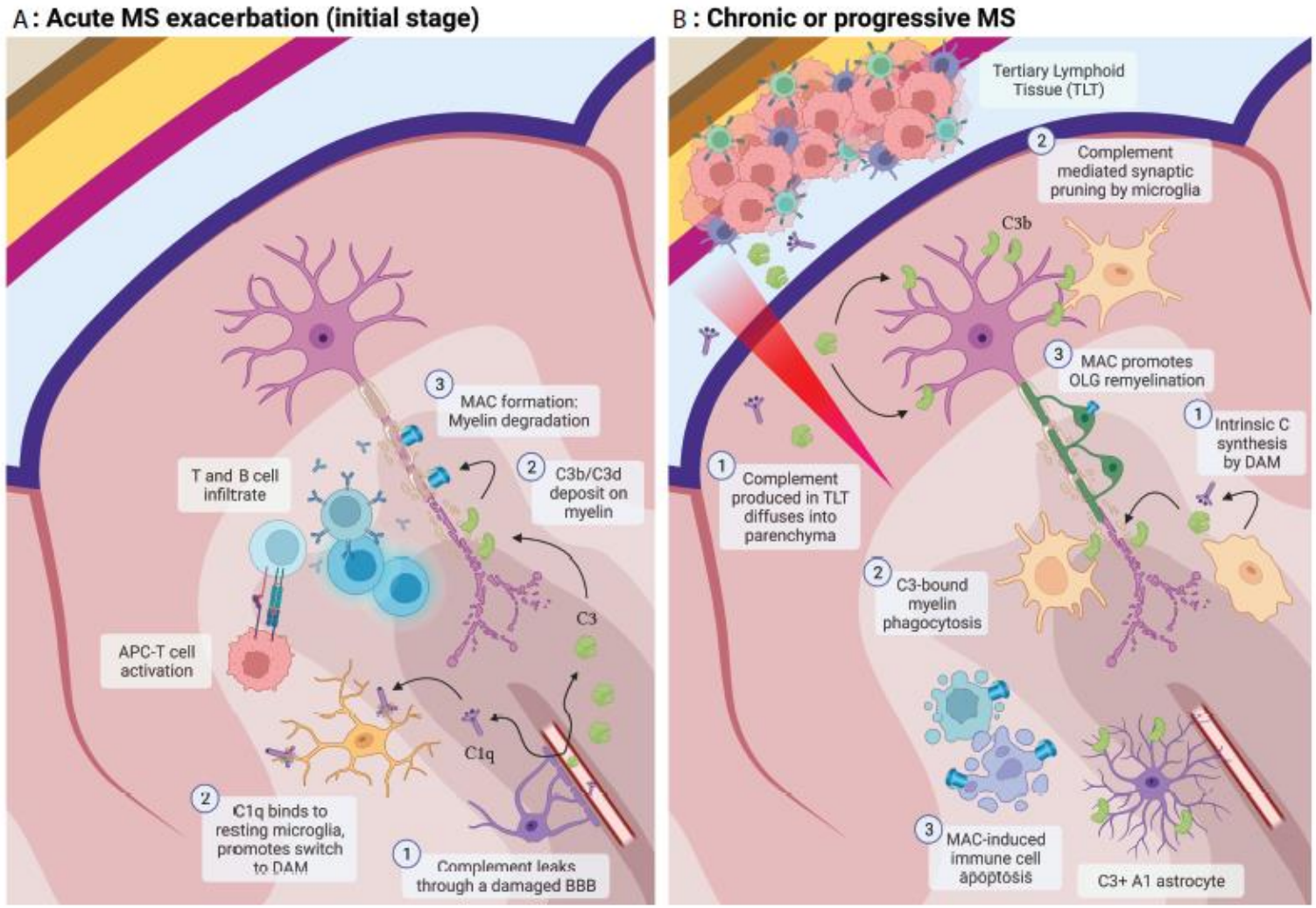
The role of the complement system in Multiple Sclerosis: A review

Front. Immunol. 13:970486.
doi: 10.3389/fimmu.2022.970486

Nil Saez-Calveras[1] and Olaf Stuve[1,2*]

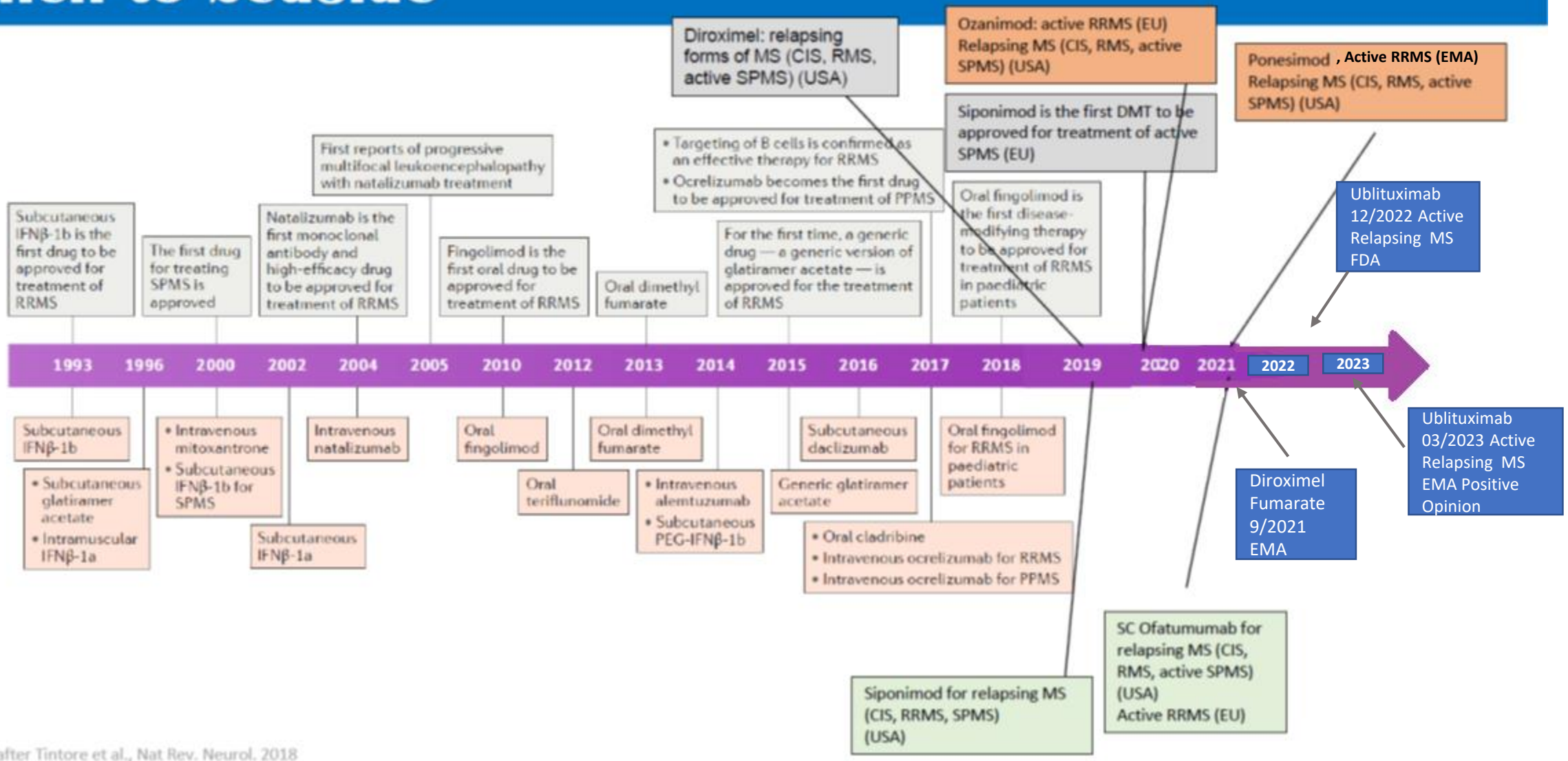
(A) Acute MS exacerbation:
1. Complement factors leak through a compromised BBB. T and B cells infiltrate the parenchyma and are activated by myeloid APCs.
2. Activated C3b and C3d deposit on myelin promoting its opsonization. C1q binds resting microglia and modulates its phenotype switch to disease-associated microglia (DAM).
3. Downstream activation of complement leads to MAC formation and damage to the myelin membrane.

(B) Progressive MS:
1. Complement and other factors are secreted by DAM and by the tertiary lymphoid tissue (TLT) and diffuse into the brain parenchyma.
2. C3-bound myelin products are opsonized by myeloid cells and activated microglia.
3. In this stage, MAC formation exerts protective effects through the apoptosis of inflammatory cells and prevention of OLG apoptosis



Η ΘΕΡΑΠΕΙΑ

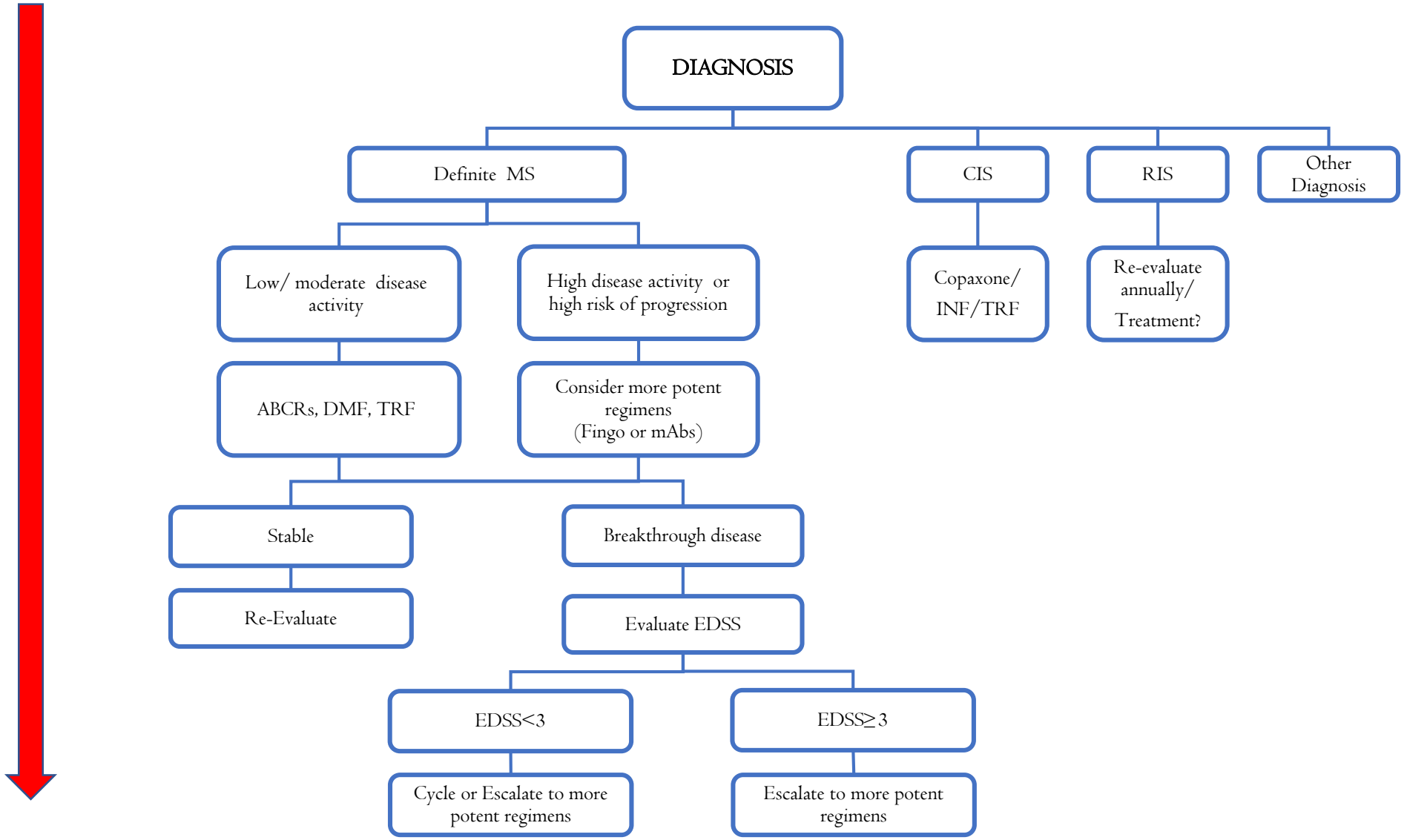
Treatment of multiple sclerosis – success from bench to bedside



Modified after Tintore et al., Nat Rev. Neurol. 2018

ΠΡΩΤΟΚΟΛΛΟ ΘΕΡΑΠΕΙΑΣ- ΚΛΙΜΑΚΩΤΗ ΠΡΟΣΕΓΓΙΣΗ

ESCALATION THERAPY

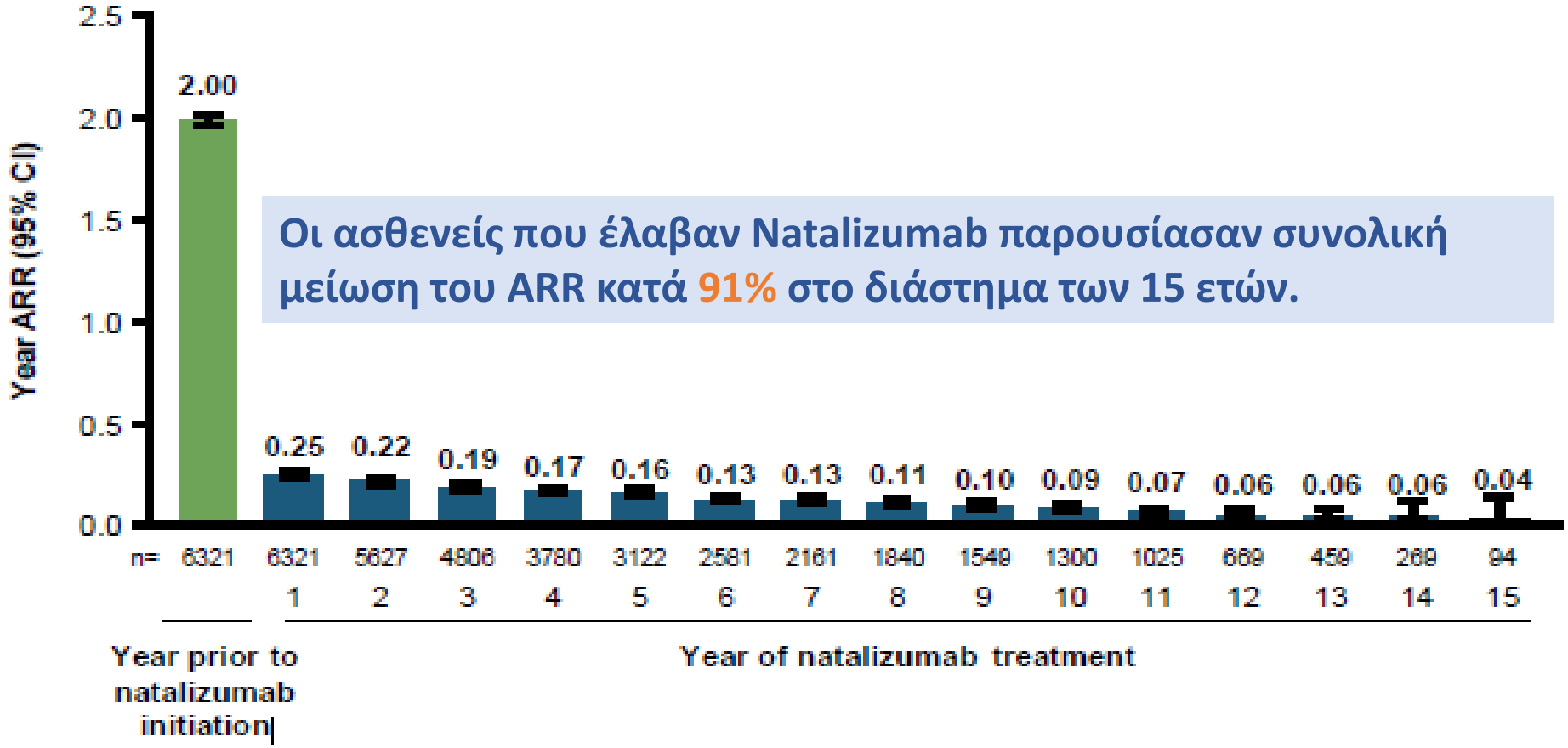


Ευρωπη, ΕΝΕ, Κύπρος

Μελέτη TOP, 15 έτη: επιδεικνύει το όφελος που προσφέρει το natalizumab μακροπρόθεσμα

EPO-658

Natalizumab Observational Program: Long-term Safety and Effectiveness in Relapsing-Remitting Multiple Sclerosis over 15 Years



Οι ασθενείς που έλαβαν Natalizumab παρουσίασαν συνολική μείωση του ARR κατά 91% στο διάστημα των 15 ετών.

Ο ARR κατά τη διάρκεια κάθε έτους θεραπείας με natalizumab

Trojano et al, EPO-658, EAN, 07-2023

MSJ Experimental Translational Clinical

Original Research Paper

The ACROSS study: Long-term efficacy of fingolimod in patients with relapsing–remitting multiple sclerosis

T Derfuss, J Sastre-Garriga, X Montalban, M Rodegher, J Wuerfel, L Gaetano, D Tomic, A Azmon, C Wolf and L Kappos

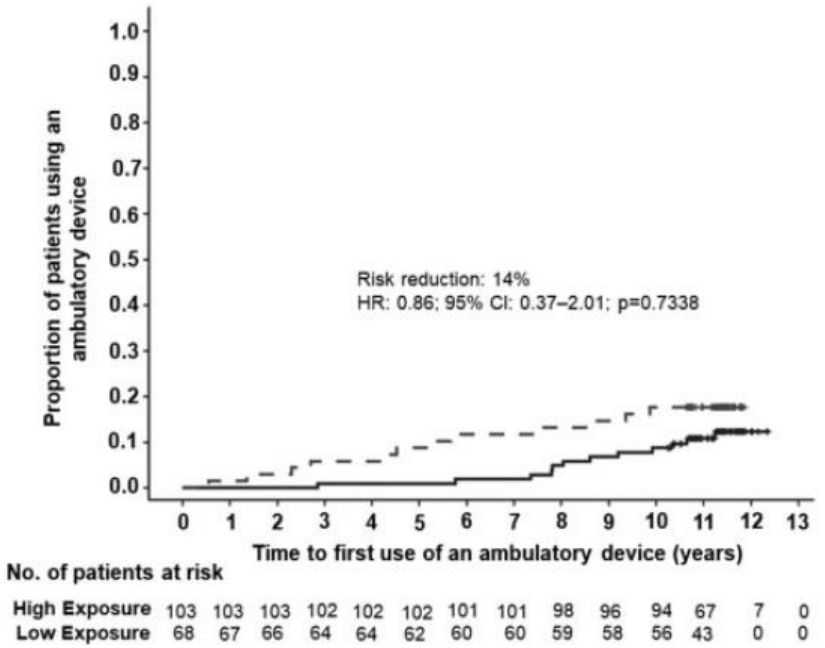
Multiple Sclerosis Journal—Experimental, Translational and Clinical

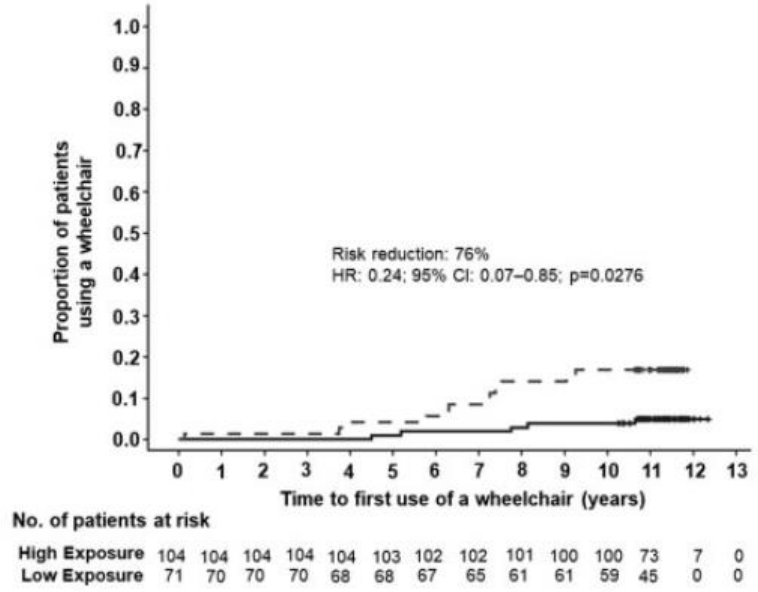
January–March 2020, 1–10

DOI: 10.1177/2055217320907951

Methods: ACROSS was a cross-sectional follow-up study of patients originally enrolled in a Phase 2 fingolimod proof-of-concept study (NCT00333138). Disability and magnetic resonance imaging-related outcomes were assessed in patients grouped according to fingolimod treatment duration, based on an arbitrary cut-off: ≥8 years (high exposure) and <8 years (low exposure).

Results: Overall, 175/281 (62%) patients participated in ACROSS; 104 (59%) of these were classified "high exposure." At 10 years, patients in the high-exposure group had smaller increases in Expanded Disability Status Scale (+0.55 vs. +1.21), and lower frequencies of disability progression (34.7% vs. 56.1%), wheelchair use (4.8% vs. 16.9%), or transition to secondary progressive multiple sclerosis (9.6% vs. 22.5%) than those in the low-exposure group. The high-exposure patients also had less progression in most magnetic resonance imaging-related outcomes.

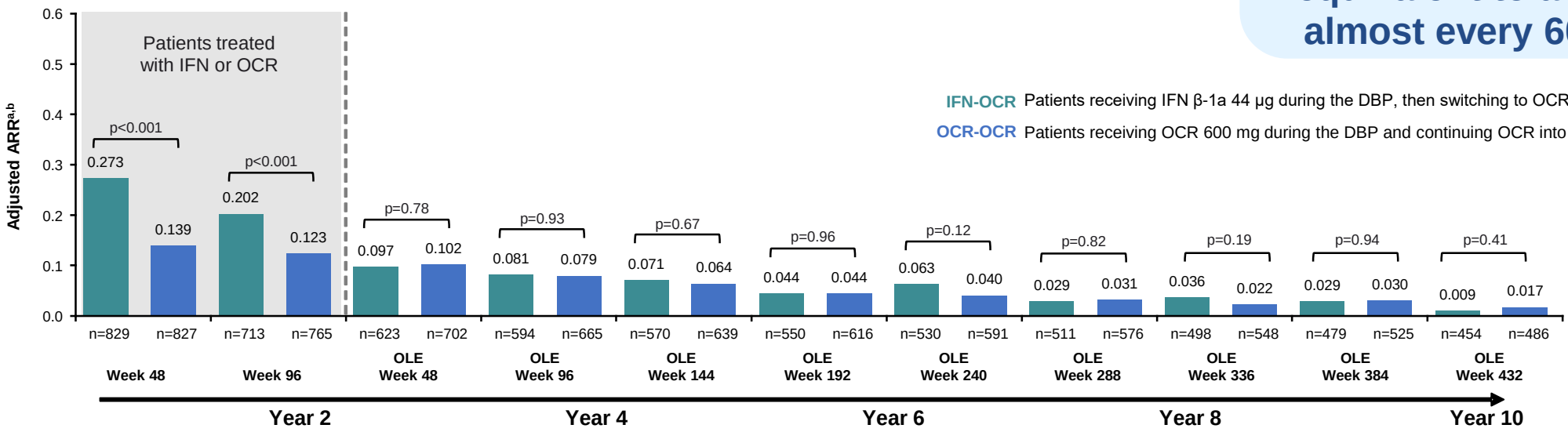




Annualised Protocol Defined Relapse Rate by Year

After 10 years in PwRMS continuously treated with OCR, the ARR (0.017) was equivalent to a relapse almost every 60 years

OPERA I/II



ARR decreased year-on-year from the pre-switch year to Year 10 in IFN–OCR switcher and was maintained at low levels in all patients treated with OCR

[a]The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment. [b]DBP year 1 and DBP year 2 data include the intention-to-treat population (number of patients available); year 3 (OLE year 1), year 4 (OLE year 2), and year 5 (OLE year 3) data include the OLE ITT population (number of patients available). Clinical cutoff date: February 5, 2018GEE Poisson Model ITT population. Adjusted ARRs from Week 48 to OLE Week 288 (Year 7.5). Adjusted by randomised treatment, study, baseline EDSS (<4.0 vs ≥4.0), geographical region (US vs ROW), year and treatment-by-year interaction.
ARR, annualised relapse rate; DBP, double-blind period; EDSS, Expanded Disability Status Scale; GEE, generalised estimating equation; IFN, interferon; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; PwRMS, patients with RMS; ROW, rest of world; RMS, relapsing multiple sclerosis.

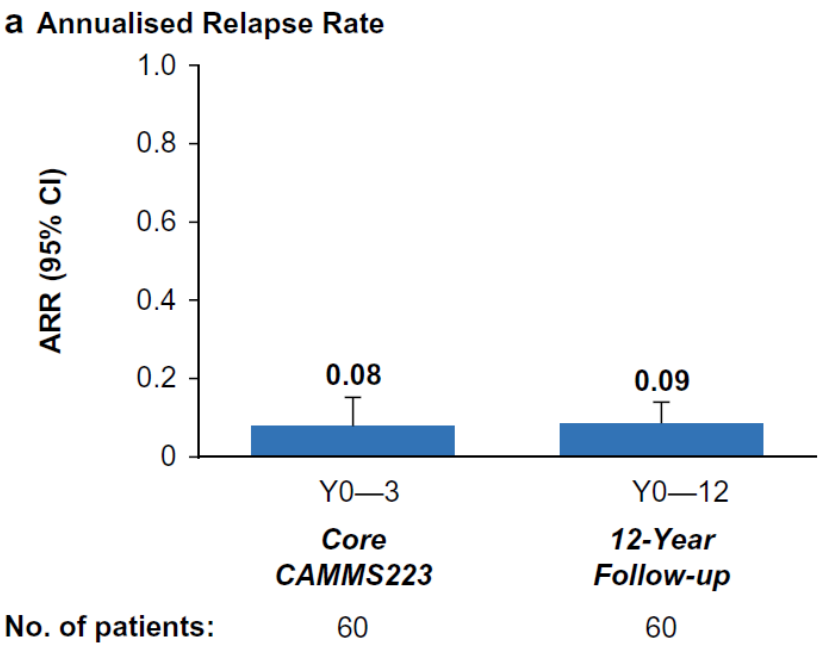
Weber MS, et al. Presented at MSMilan 2023 (P302).

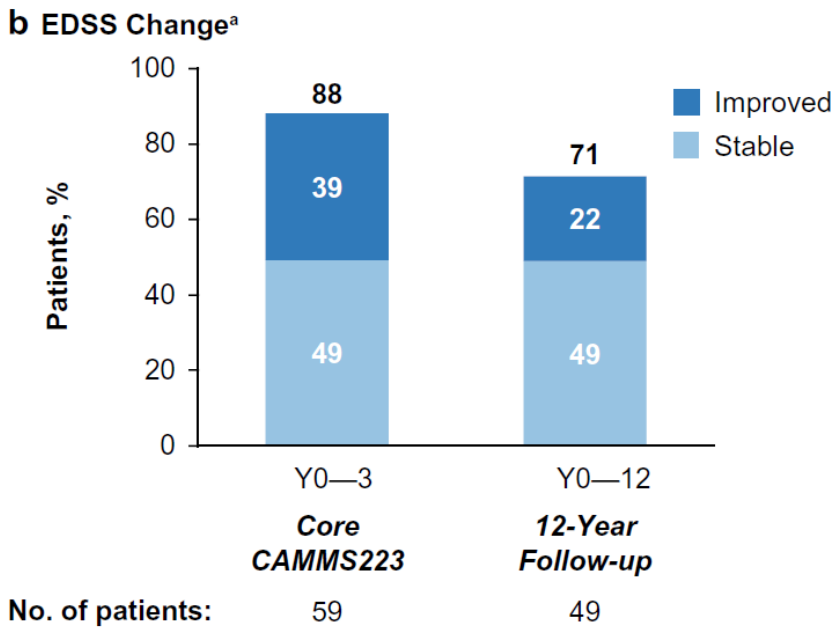
Journal of Neurology (2020) 267:3343–3353
https://doi.org/10.1007/s00415-020-09983-1

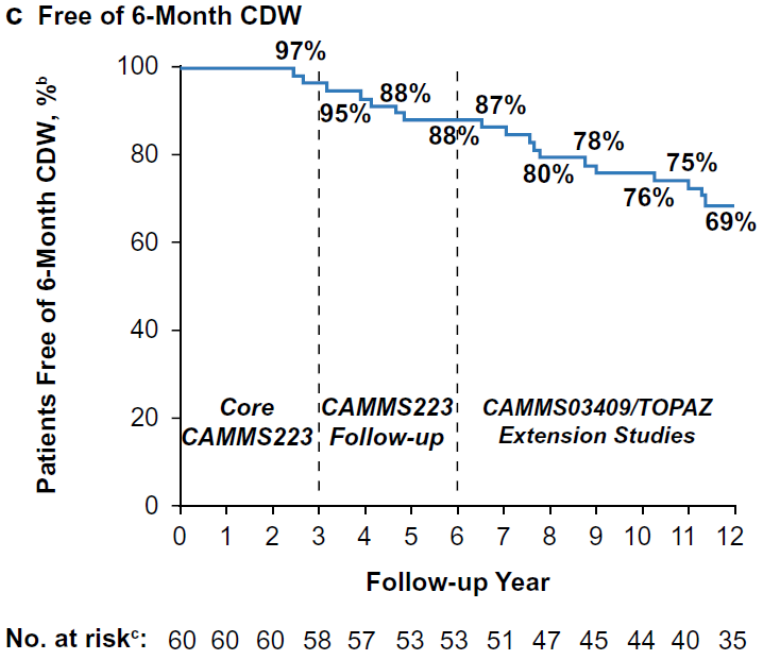
ORIGINAL COMMUNICATION

Long-term efficacy and safety of alemtuzumab in patients with RRMS: 12-year follow-up of CAMMS223

Brian Steingo[1] · Yaser Al Malik[2] · Ann D. Bass[3] · Regina Berkovich[4,5] · Matthew Carraro[6] · Óscar Fernández[7] · Carolina Ionete[8] · Luca Massacesi[9] · Sven G. Meuth[10] · Dimos D. Mitsikostas[11] · Gabriel Pardo[12] · Renata Faria Simm[13] · Anthony Traboulsee[14] · Zia Choudhry[15] · Nadia Daizadeh[15] · D. Alastair S. Compston[16] on behalf of the CAMMS223, CAMMS03409, and TOPAZ Investigators







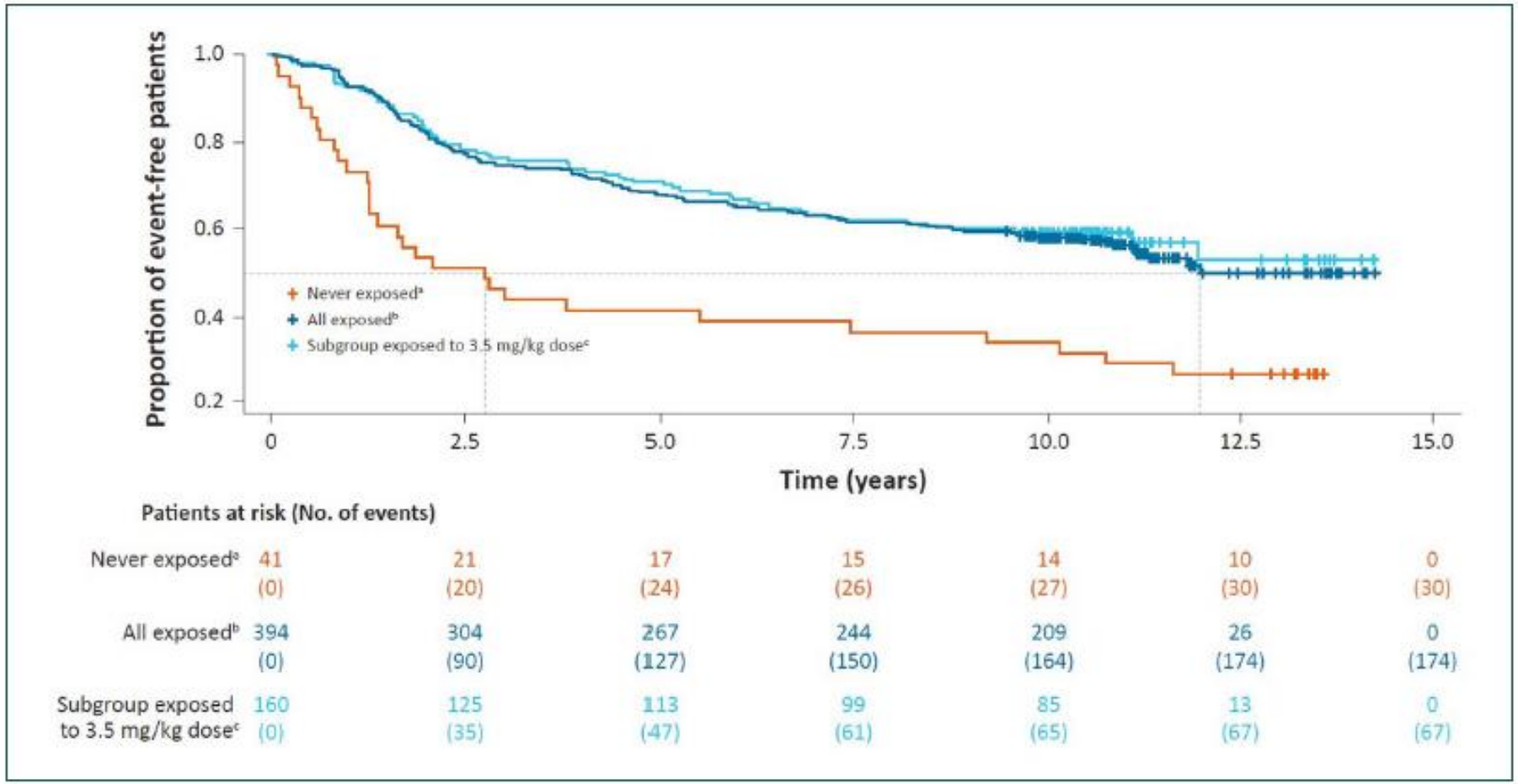
MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/ CLARITY Extension cohort of CLASSIC-MS: An ambispective study

Multiple Sclerosis Journal
2023, Vol. 29(6) 719–730
DOI: 10.1177/13524585231161494

Gavin Giovannoni, Alexey Boyko, Jorge Correale, Gilles Edan, Mark S Freedman, Xavier Montalban, Kottil Rammohan, Dusan Stefoski, Bassem Yamout, Thomas Leist, Aida Aydemir, Laszlo Borsi and Elisabetta Verdun di Cantogno



Patients at risk (No. of events)

Never exposed[a]	41 (0)	21 (20)	17 (24)	15 (26)	14 (27)	10 (30)	0 (30)
All exposed[b]	394 (0)	304 (90)	267 (127)	244 (150)	209 (164)	26 (174)	0 (174)
Subgroup exposed to 3.5 mg/kg dose[c]	160 (0)	125 (35)	113 (47)	99 (61)	85 (65)	13 (67)	0 (67)

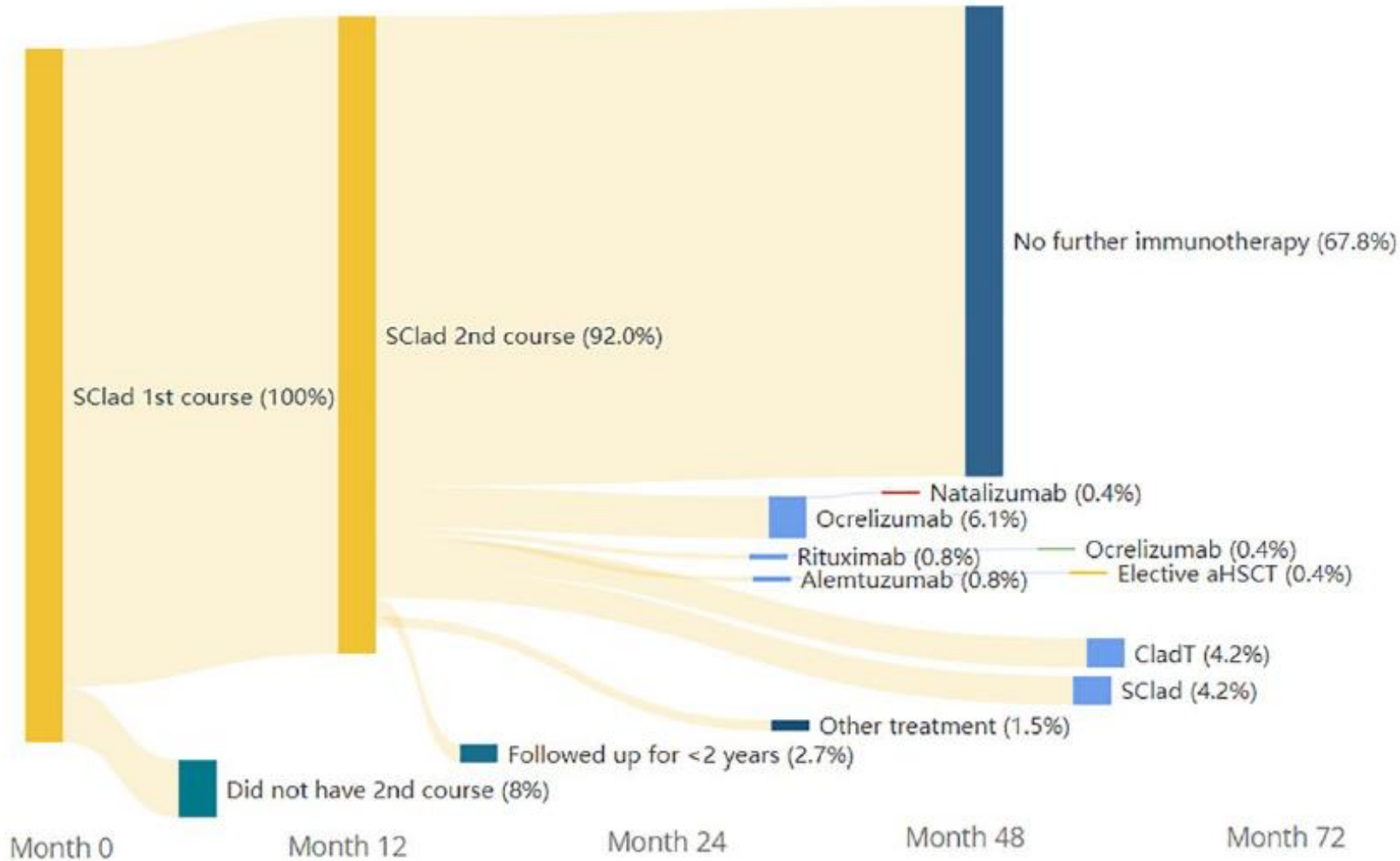
THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

Disease activity 4.5 years after starting cladribine: experience in 264 patients with multiple sclerosis

Ther Adv Neurol Disord
2023, Vol. 16: 1–12
DOI: 10.1177/
17562864231200627

Kimberley Allen-Philbey, Stefania De Trane, Amy MacDougall, Ashok Adams, Lucia Bianchi, Thomas Campion, Gavin Giovannoni, Sharmilee Gnanapavan, David W. Holden, Monica Marta, Joela Mathews, Benjamin P. Turner, David Baker and Klaus Schmierer



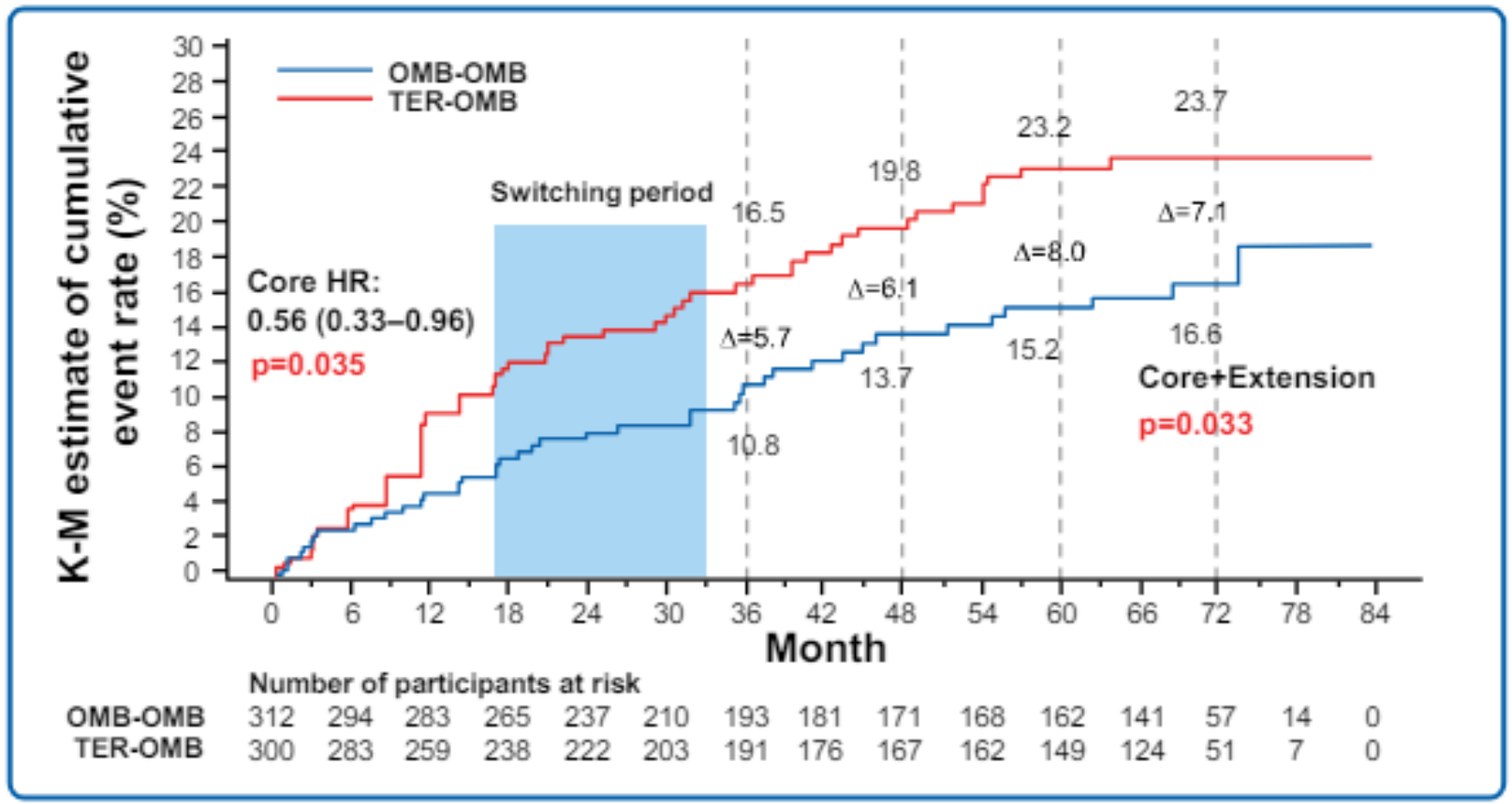
Oral presentation: S31.003
S31: Multiple Sclerosis – Therapeutics and Clinical Decision Making
Wednesday, April 17 – 1:24 PM

Gabriel Pardo
gabriel-pardo@omrf.org

Longer-Term (up to 6 Years) Efficacy of Ofatumumab in People With Recently Diagnosed and Treatment-Naive Relapsing Multiple Sclerosis

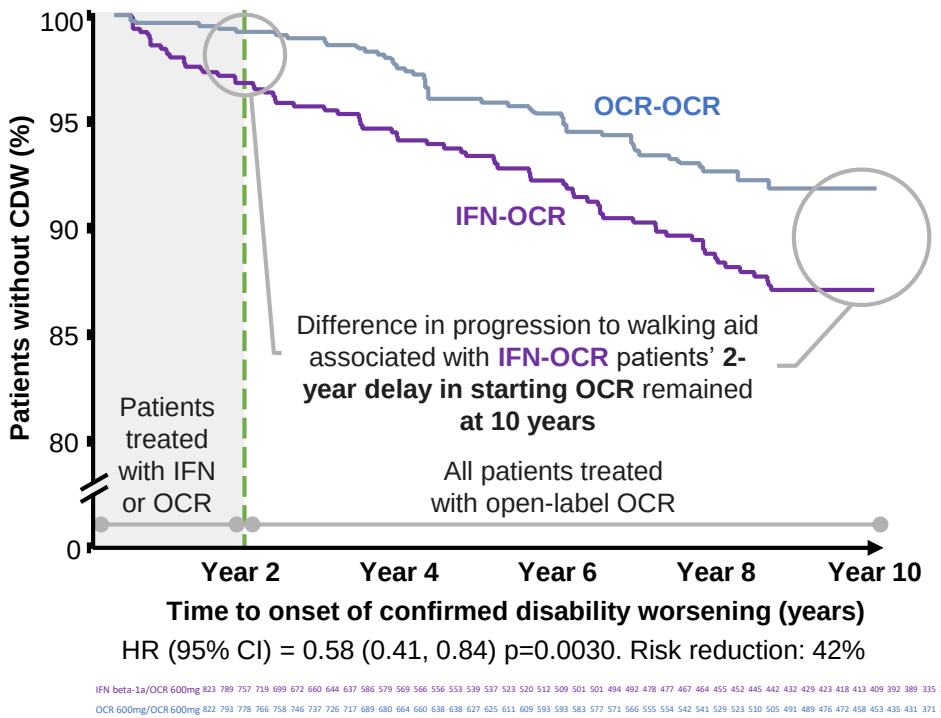
Gabriel Pardo[1], Stephen L. Hauser[2], Amit Bar-Or[3], Ralf Gold[4], Xavier Montalban[5], Jeffrey A. Cohen[6], Derrick Robertson[7], Carrie M. Hersh[8], Robert T. Naismith[9], Kumaran Deiva[10], Alit Bhatt[11], Haoyi Fu[12], Ibolya Boer[13], Sven G. Meuth[14], Anne H. Cross[15], Jutta Gärtner[16], Ludwig Kappos[17]

Cumulative event rate – 6mCDW



Early initiation of Ocrelizumab lowers by 42% the risk of requiring a walking aid in RMS

After 10 years, >90% PwRMS treated with continuous ocrelizumab did not require a walking aid



91.9% of OCR-OCR patients did not require a walking aid at **10 years**

OPERA I/II

Over 10 years, in PwRMS there was a 42% reduction in the risk of requiring a walking aid in those who initiated ocrelizumab earlier vs delayed treatment

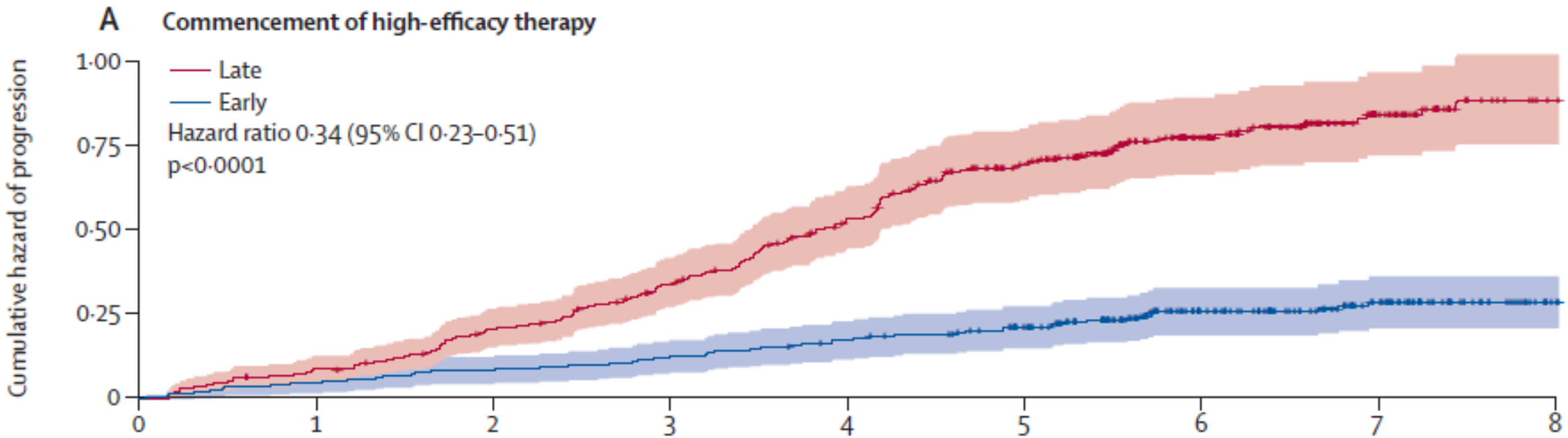
CDW, confirmed disability worsening; CI, confidence interval; HR, hazard ratio; IFN, interferon β-1a; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; PwRMS, patients with relapsing multiple sclerosis; RMS, relapsing multiple sclerosis.

Hauser SL, *et al*. ECTRIMS 2023 (P304).

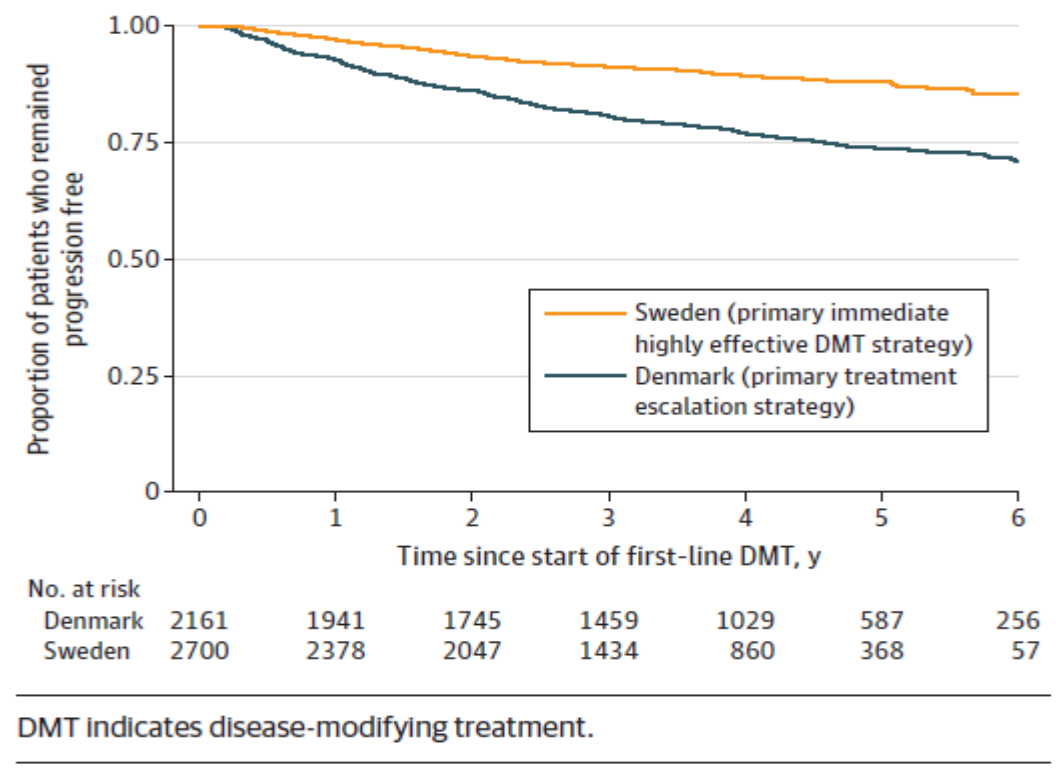
Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study

*Anna He, Bernd Merkel, James William L Brown, Lana Zhovits Ryerson, Ilya Kister, Charles B Malpas, Sifat Sharmin, Dana Horakova, Eva Kubala Havrdova, Tim Spelman, Guillermo Izquierdo, Sara Eichau, Maria Trojano, Alessandra Lugaresi, Raymond Hupperts, Patrizia Sola, Diana Ferraro, Jan Lycke, Francois Grand'Maison, Alexandre Prat, Marc Girard, Pierre Duquette, Catherine Larochelle, Anders Svenningsson, Thor Petersen, Pierre Grammond, Franco Granella, Vincent Van Pesch, Roberto Bergamaschi, Christopher McGuigan, Alasdair Coles, Jan Hillert, Fredrik Piehl, Helmut Butzkueven, Tomas Kalincik, on behalf of the MSBase study group**

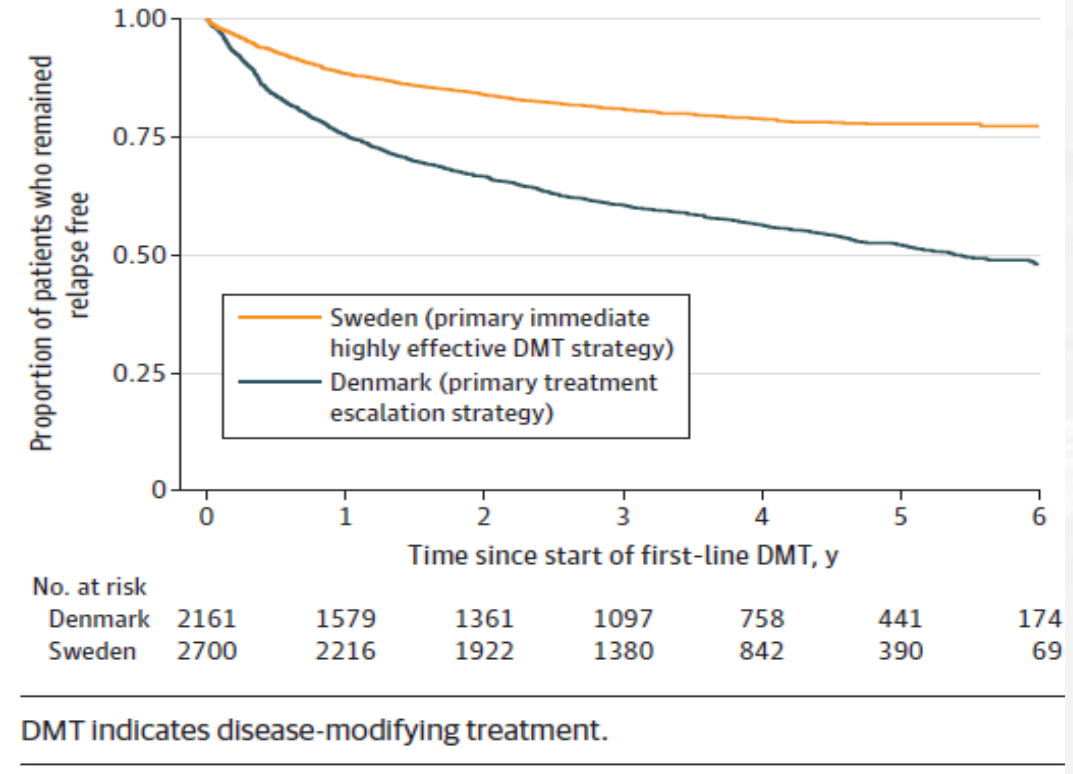
Lancet Neurol 2020; 19: 307–16



Πρώιμη θεραπεία με φάρμακα υψηλής αποτελεσματικότητας – ένα διαρκές πλεονέκτημα



Time to Confirmed Disability Progression by Treatment Strategy Cohort



Time to First Relapse by Treatment Strategy Cohort

Spelman et al, *JAMA Neurol*. 2021;78(10):1197-1204.

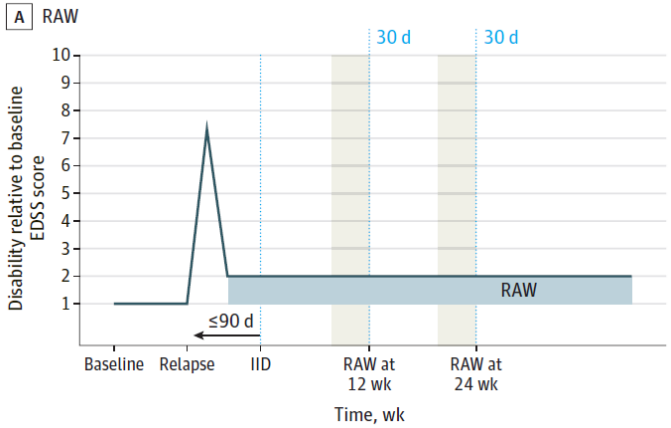
JAMA Neurology | Original Investigation

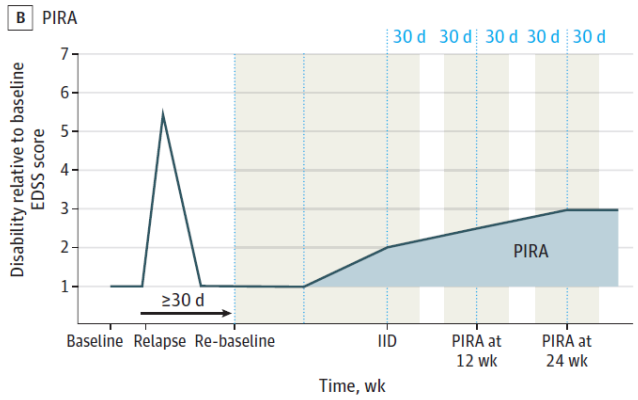
Progression Independent of Relapse Activity (PIRA)

Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials

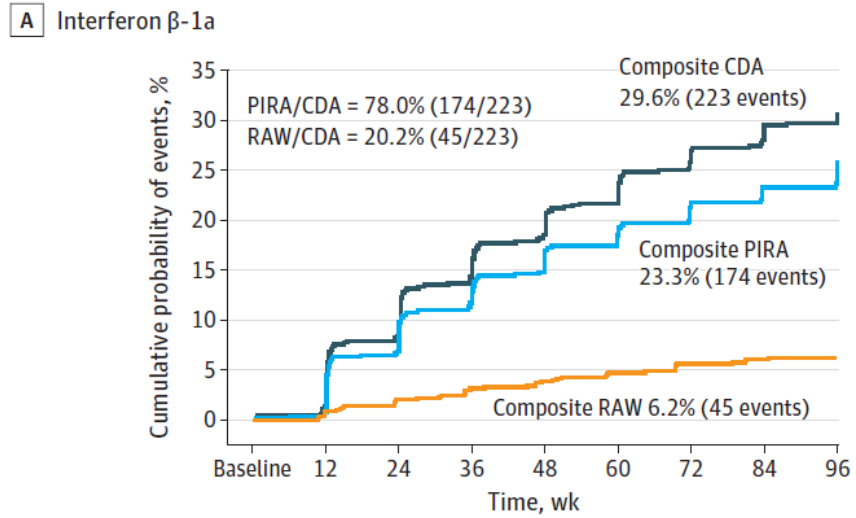
Ludwig Kappos, MD; Jerry S. Wolinsky, MD; Gavin Giovannoni, PhD; Douglas L. Arnold, MD; Qing Wang, PhD; Corrado Bernasconi, PhD; Fabian Model, PhD; Harold Koendgen, MD; Marianna Manfrini, MD; Shibeshih Belachew, MD; Stephen L. Hauser, MD

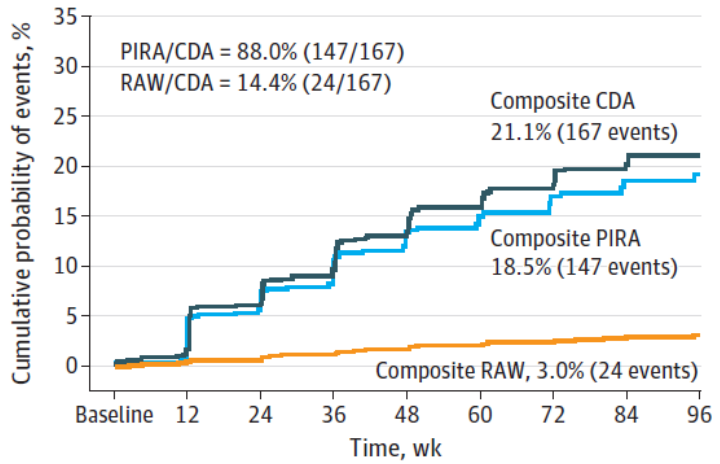
JAMA Neurol. 2020;77(9):1132-1140. doi:10.1001/jamaneurol.2020.1568
Published online June 8, 2020.





CONCLUSIONS AND RELEVANCE Most disability accumulation in RMS is not associated with overt relapses. This indicates an underlying progression in this typical RMS population and challenges the current clinical distinction of relapsing and progressive forms of multiple sclerosis. Ocrelizumab was superior to interferon β-1a in preventing both RAW and PIRA.



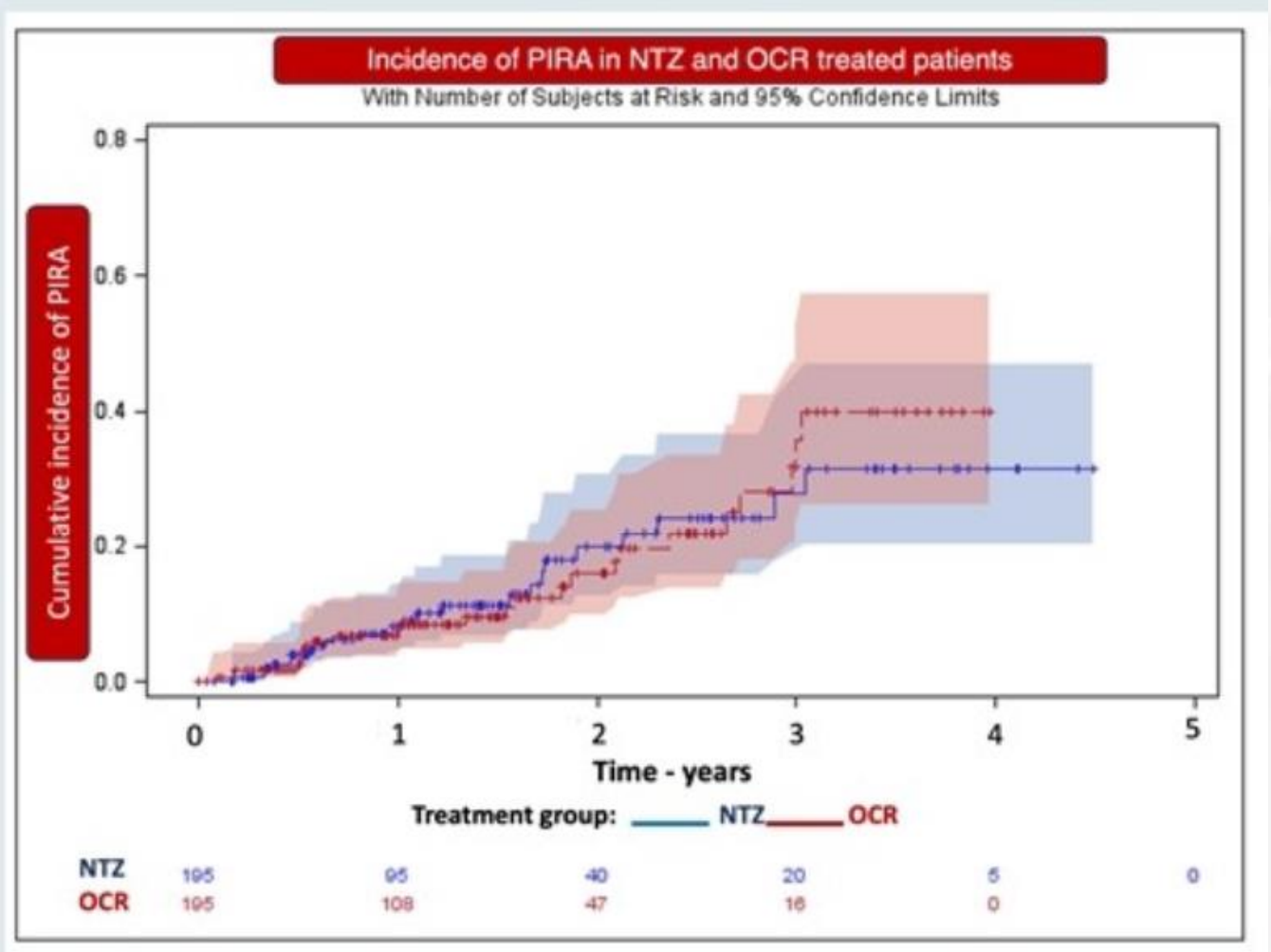


MSMilan2023
9th Joint ECTRIMS-ACTRIMS Meeting
11–13 October 2023 | Milan, Italy

The comparative effectiveness of natalizumab and ocrelizumab in naïve relapsing remitting multiple sclerosis: the impact on relapse dependent and relapse independent disability progression

P326
Therapy – Real world evidence (RWE) and MS registries

P. Iaffaldano[1], G. Lucisano[2], T. Guerra[1], D. Paolicelli[1], M. Inglese[3, 4], M. Foschi[5], F. Patti[6], F. Granella[7], S. Romano[8], P. Cavalla[9], G. De Luca[10], P. Gallo[11], P. Bellantonio[12], A. Gallo[13], S. Montepietra[14], A. di Sapio[15], M. Vianello[16], R. Quatrale[17], D. Spitalieri18, R. Clerici[19], V. Torri Clerici[20], E. Cocco[21], V. Brescia Morra[22], G. A. Marfia[23], M. Filippi[24], M.P. Amato[25], M. Trojano[1], on behalf of the Italian MS Register.



Curr Treat Options Neurol (2021) 23:19
DOI 10.1007/s11940-021-00677-1

Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Πρώτα αποτελέσματα αναμένονται 2025 +

Early Aggressive Treatment Approaches for Multiple Sclerosis

Alexandra Simpson, MD[1]
Ellen M. Mowry, MD, MCR[1]
Scott D. Newsome, DO[1,2,*]

	TREAT-MS (TRaditional versus Early Aggressive Therapy for MS)	DELIVER-MS (Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for the treatment of Relapsing-remitting MS)
Intervention/treatment groups	Early aggressive therapies • Natalizumab • Alemtuzumab • Ocrelizumab • Rituximab • Ofatumumab • Cladribine Traditional therapies • Subcutaneous, intramuscular, and pegylated interferon • Glatiramer acetate • Teriflunomide • Dimethyl fumarate, diroximel fumarate • Fingolimod, siponimod, ozanimod	Early highly effective therapies • Natalizumab • Alemtuzumab • Ocrelizumab • Rituximab • Ofatumumab Escalation therapies • Beta interferon • Glatiramer acetate • Teriflunomide • Dimethyl fumarate, diroximel fumarate • Fingolimod, siponimod, ozanimod • Cladribine

ΤΕΛΕΥΤΑΙΑ ΔΕΔΟΜΕΝΑ

ANNALS of Clinical and Translational Neurology
AMERICAN NEUROLOGICAL ASSOCIATION
Open Access

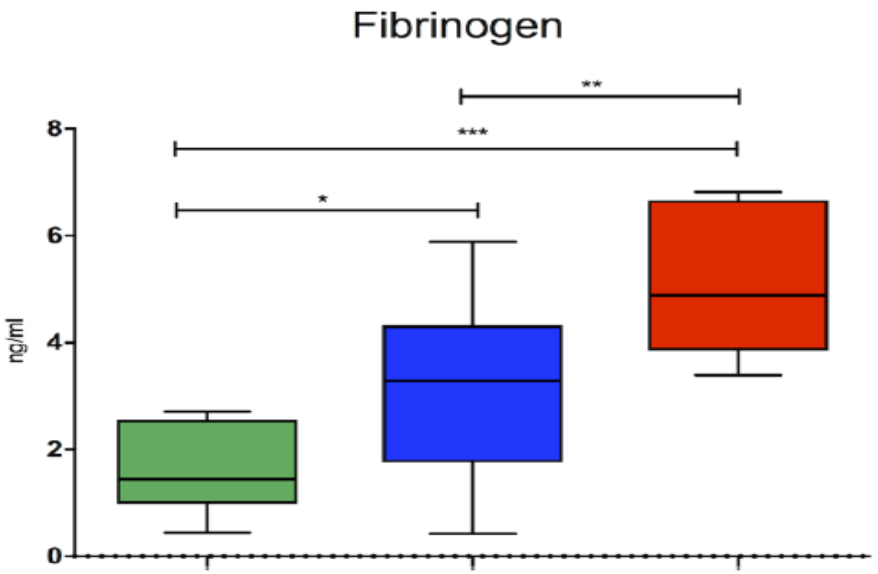
RESEARCH ARTICLE

Iron homeostasis, complement, and coagulation cascade as CSF signature of cortical lesions in early multiple sclerosis

Roberta Magliozzi[1,2], Simon Hametner[3], Francesco Facchiano[4], Damiano Marastoni[1], Stefania Rossi[1,4], Marco Castellaro[1], Alberto Poli[1], Federico Lattanzi[1], Andrea Visconti[5], Richard Nicholas[2], Richard Reynolds[2], Salvatore Monaco[1], Hans Lassmann[3] & Massimiliano Calabrese[1]

First Inflammation Pattern

Fibrinogen deposition has been previously found to be associated with blood-brain barrier disruption, neuroinflammation, and neurodegeneration in MS.



frontiers in Immunology

Coagulation/Complement Activation and Cerebral Hypoperfusion in Relapsing-Remitting Multiple Sclerosis

STUDY PROTOCOL
published: 27 October 2020
doi: 10.3389/fimmu.2020.548604

Tatiana Koudriavtseva[1*], Annunziata Stefanile[1], Marco Fiorelli[2], Caterina Lapucci[3], Svetlana Lorenzano[2], Silvana Zannino[1], Laura Conti[1], Giovanna D'Agosto[4], Fulvia Pimpinelli[4], Enea Gino Di Domenico[4], Chiara Mandoj[1], Diana Giannarelli[5], Sara Donzelli[6], Giovanni Blandino[6], Marco Salvetti[7] and Matilde Inglese[3,8]

- Innate immunity, plays a relevant role in MS pathogenesis. It represents the immediate non-specific defense against infections through the intrinsic effector mechanism "immunothrombosis" linking inflammation and coagulation.
- Decreased cerebral blood volume (CBV), cerebral blood flow (CBF)/ regional CBF, and prolonged mean transit time (MTT) have been widely demonstrated by MRI in MS patients.
- Coagulation/complement and platelet activation during MS relapse, could be related to CBF decrease.

Immunohistochemical study of vascular injury in acute multiple sclerosis

A J Wakefield, L J More, J Difford, J E McLaughlin

J Clin Pathol 1994;47:129–133

- Early vascular endothelial cell activation which may progress to "vasculitis" and vascular occlusion with fibrin deposition was identified.
- The vascular changes were seen before cerebral parenchymal reaction and demyelination and were not seen in control cerebral tissues.
- It was proposed that vascular endothelial cell activation may be an early and pivotal event in the evolution of multiple sclerosis,

ANNALS of Clinical and Translational Neurology
Open Access
RESEARCH ARTICLE

Iron homeostasis, complement, and coagulation cascade as CSF signature of cortical lesions in early multiple sclerosis

Roberta Magliozzi[1,2], Simon Hametner[3], Francesco Facchiano[4], Damiano Marastoni[1], Stefania Rossi[1,4], Marco Castellaro[1], Alberto Poli[1], Federico Lattanzi[1], Andrea Visconti[5], Richard Nicholas[2], Richard Reynolds[2], Salvatore Monaco[1], Hans Lassmann[3] & Massimiliano Calabrese[1]

Second Inflammation Pattern

- Compartmentalized inflammation within the meninges of MS patients is spatially related to subpial/ perivascular demyelination, which accounts for about 70% of GM demyelination in progressive MS and neuronal/glial alterations in the adjacent GM, following a “surface-in" gradient from the pial surface toward the WM.
- Regional differences in CSF flow might facilitate focal or diffuse intrathecal trapping of immune cells and stasis of inflammatory molecules, which may diffuse through the pial surface toward the inner cortical layers/WM.

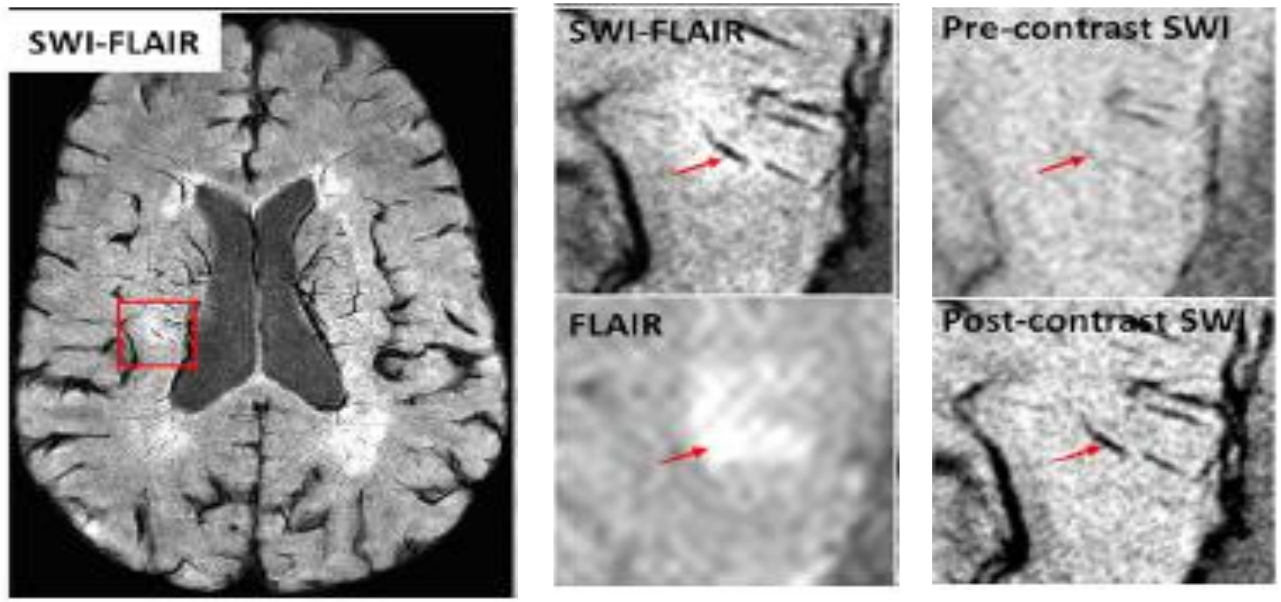
frontiers in Neurology

An Overview of Venous Abnormalities Related to the Development of Lesions in Multiple Sclerosis

REVIEW
published: 26 April 2021
doi: 10.3389/fneur.2021.561458

E. Mark Haacke[1*], Yulin Ge[2], Sean K. Sethi[1], Sagar Buch[1] and Paolo Zamboni[3]

- Veins and venules in or at a distance from active MS lesions frequently exhibit an inflammatory lymphocytic reaction located only in the vessel wall (a form of local venous vasculitis or cerebral venulitis).
- Collagenosis of the veins could prevent exchange between the surrounding CSF and the venous blood that may act as a drainage for waste products of the brain.
- These effects may affect the function of what is referred to today as the glymphatic system (an increase in transmural pressure prevents the usual flow of metabolic wastes into the venous system).



EXPERT OPINION ON EMERGING DRUGS
2020, VOL. 25, NO. 4, 377–381
https://doi.org/10.1080/14728214.2020.1822817

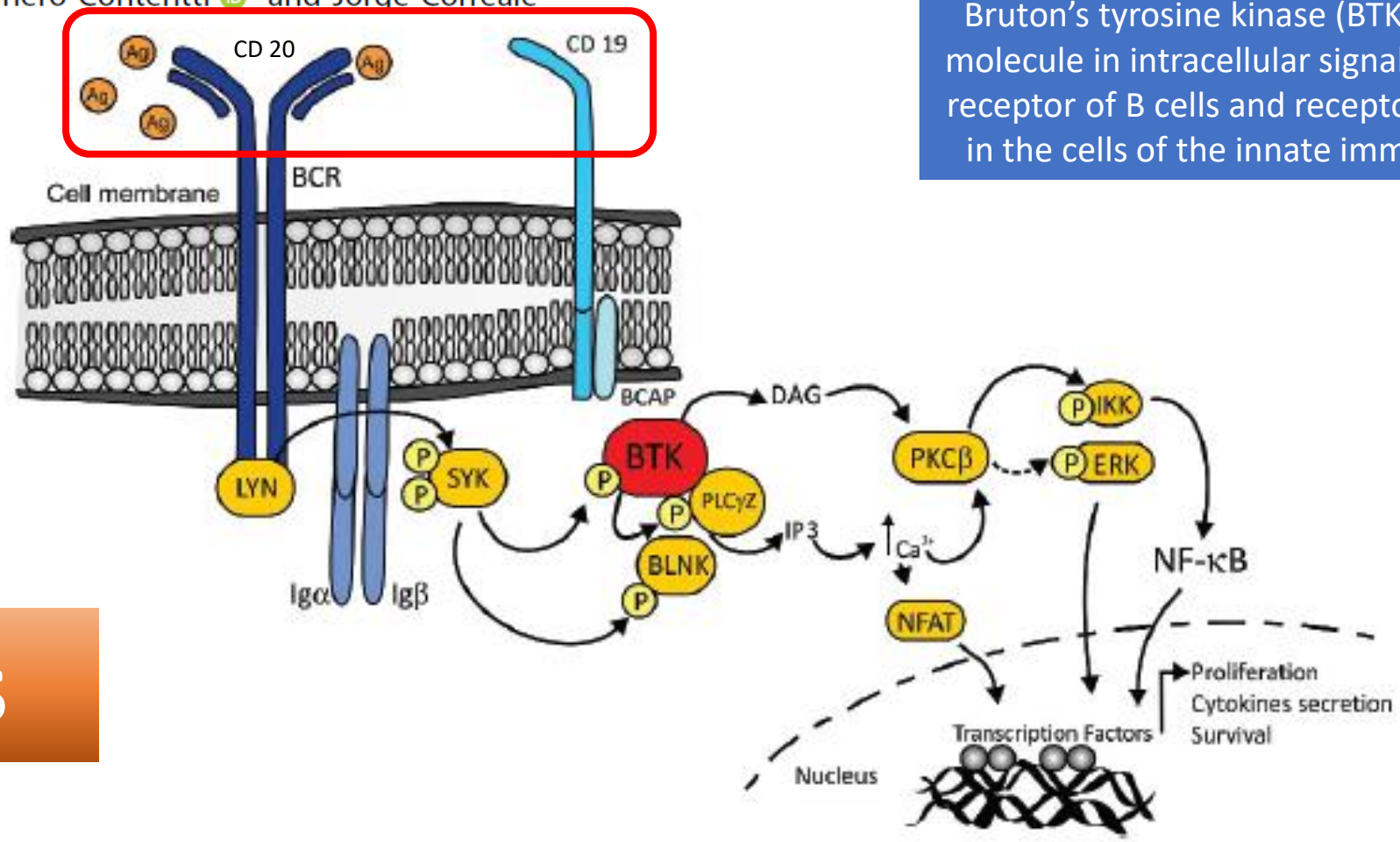
Taylor & Francis
Taylor & Francis Group

EDITORIAL

Bruton's tyrosine kinase inhibitors: a promising emerging treatment option for multiple sclerosis

Edgar Carnero Contentti [a] and Jorge Correale [b]

Bruton's tyrosine kinase (BTK) is a critical molecule in intracellular signalling from the receptor of B cells and receptors expressed in the cells of the innate immune system



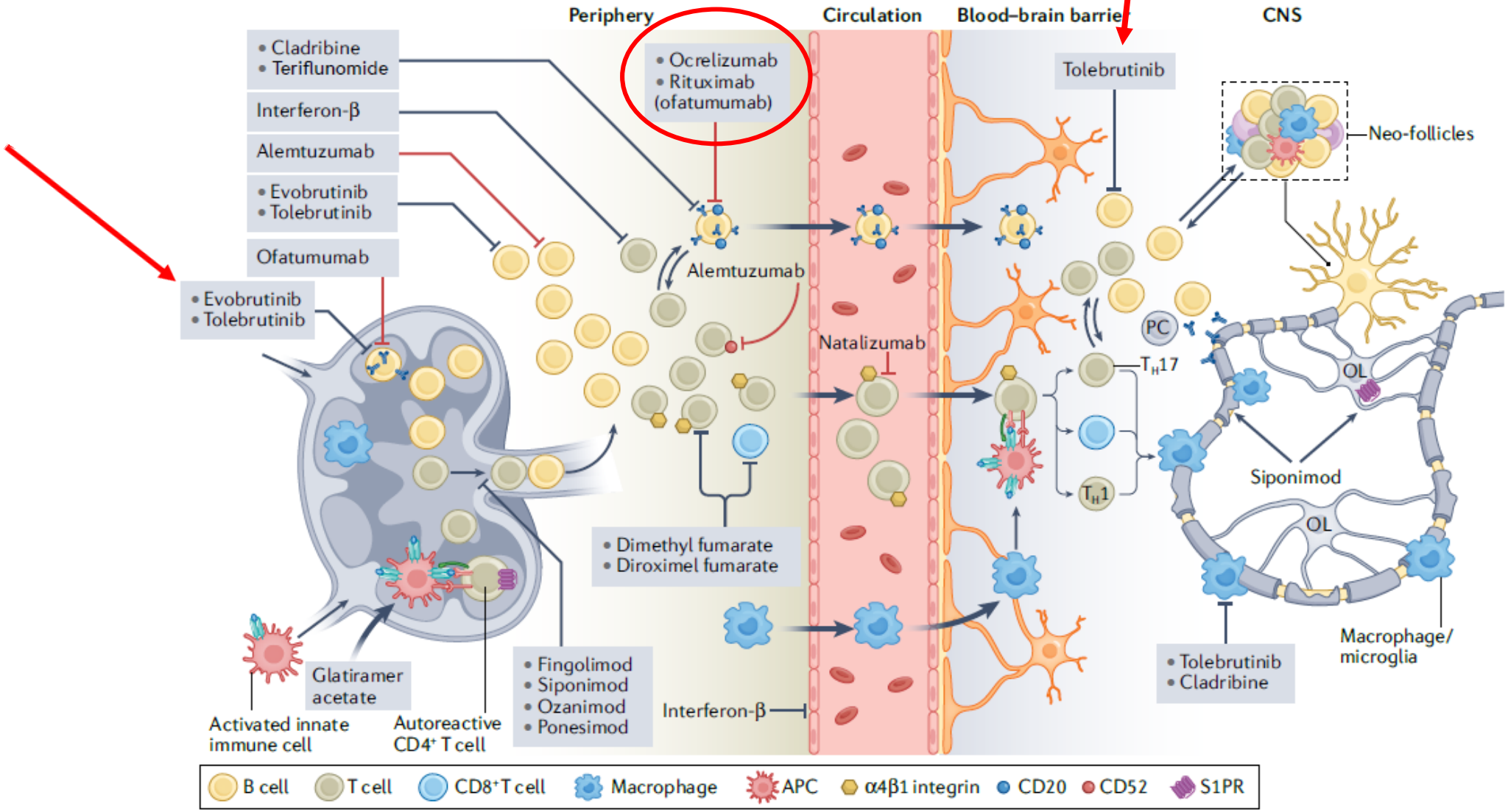
BTKs

Thinking outside the box: non-canonical targets in multiple sclerosis

Laura Bierhansl[1], Hans-Peter Hartung[2,3,4], Orhan Aktas[2], Tobias Ruck[2], Michael Roden[5,6,7] and Sven G. Meuth[2]✉

NATURE REVIEWS | DRUG DISCOVERY VOLUME 21 | AUGUST 2022 | 579

Bruton's tyrosine kinase inhibitors, which are very small molecules, address not only the adaptive but also the innate immune system and can reach the CNS easily



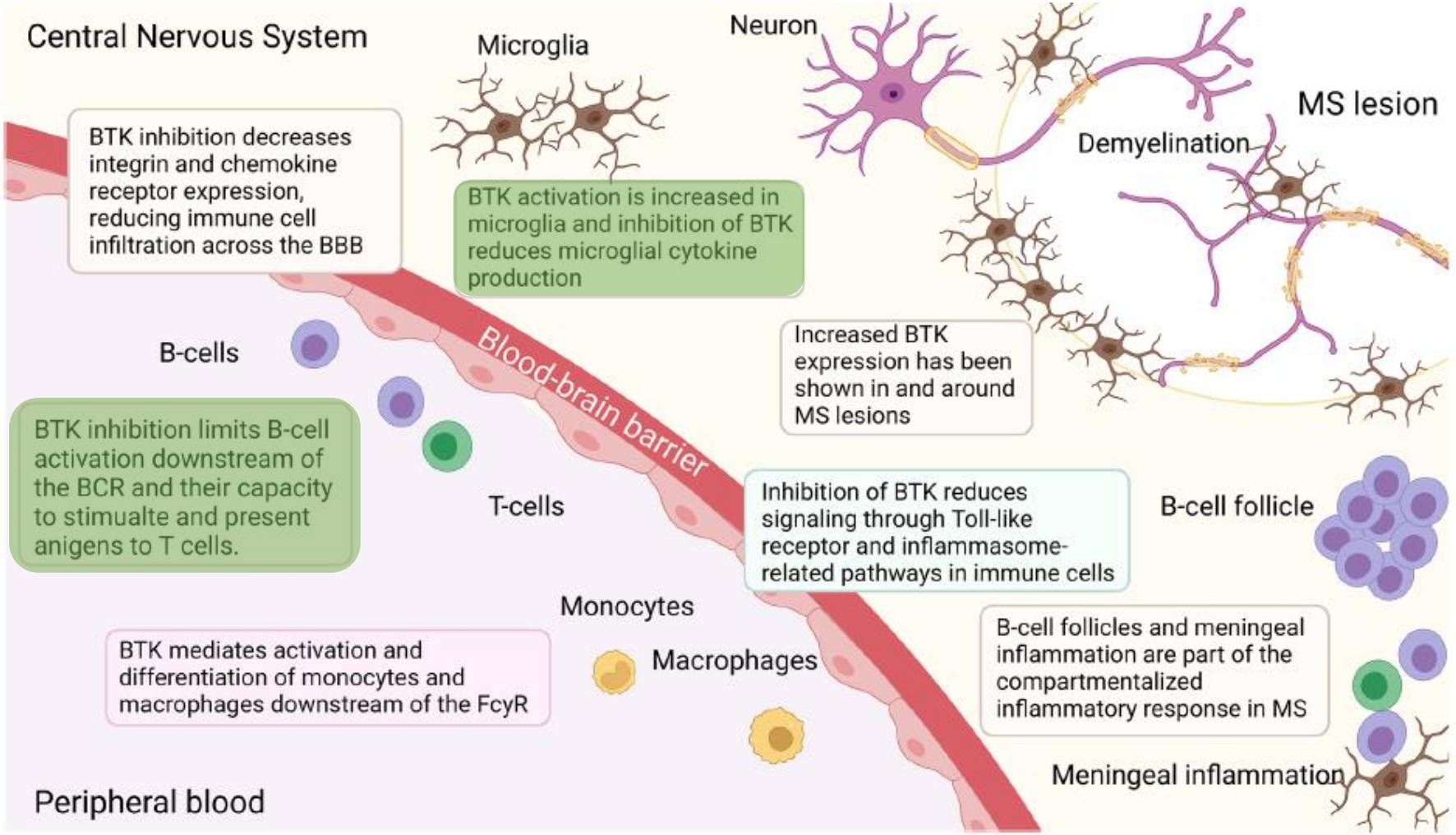
Current Neurology and Neuroscience Reports (2022) 22:721–734
https://doi.org/10.1007/s11910-022-01229-z

DEMYELINATING DISORDERS (J. BERNARD AND M. CAMERON, SECTION EDITORS)

Bruton's Tyrosine Kinase Inhibition in Multiple Sclerosis

Raphael Schneider[1,2] · Jiwon Oh[1,2]

Important milestones in the drug therapy of MS have been achieved in the last 10 years. While the focus was initially on controlling acute relapses of MS, efforts are increasingly moving in the direction of establishing therapy options for progressive disease. Great hopes are pinned on the class of **Bruton's tyrosine kinase inhibitors, which address not only the adaptive but also the innate immune system**, which is thought to be responsible for the maintenance of chronic MS disease progression



cells

MDPI

Review

Bruton's Tyrosine Kinase Inhibitors: A New Generation of Promising Agents for Multiple Sclerosis Therapy

Antonio García-Merino

Cells **2021**, *10*, 2560. https://doi.org/10.3390/cells10102560

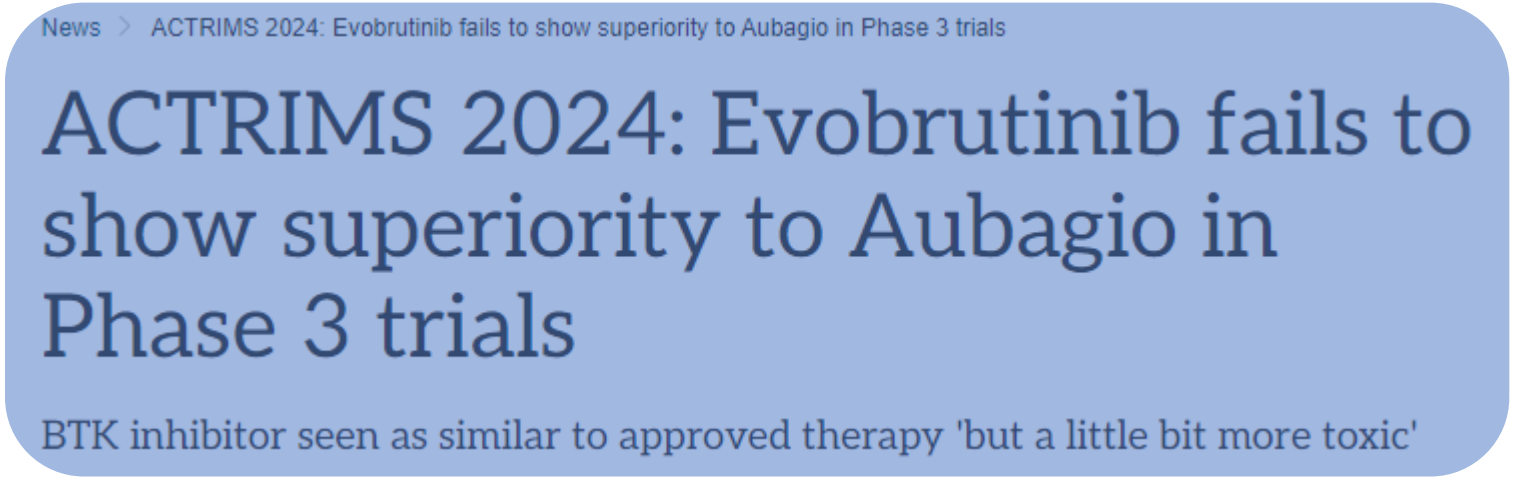
- Over the last three decades, immune therapy for MS has passed important milestones, effectively controlling clinical and MRI activity, even in patients with significantly active disease, slowing the accumulation of disability and delaying entry into the secondary progressive phase
- Despite modest advances with SPMS or PPMS, progression has been a stumbling block for therapy. Progression in MS is complex and is thought to depend on different factors, some of which are not well understood. Persistent inflammation within the CNS stands out as one of the candidate factors. Inflammation accompanies myelin damage alongside the evolution of the disease
- In chronic stages, BBB permeability is restored, preventing the entry of therapeutic agents. Compartmentalized or "trapped" inflammation in the CNS has become an important challenge for therapy, and it may be a major contributor to myelin and axonal damage.
- For MS, the availability of a family of new drugs that can reach therapeutic concentrations inside the CNS, counteract the inflammation driven by B cells, and modulate the critical players in innate immunity, such as macrophages and microglia, is a therapeutic promise.
- ***If BTK inhibitors effectively control persistent compartmentalized CNS inflammation, this could represent a great step toward the prevention of MS progression***

Name/ company	Clinical studies	MS type	Comparator	Outcomes	Status
Evobrutinib EMD Serono	Phase 2, RDB NCT02975349 (267 patients)	RRMS	Evobrutinib vs placebo	Significantly fewer enhancing lesions during weeks 12 through 24 than those who received placebo	Active, has results; estimated completion February 2025
	Phase 3, RDB NCT04338022/NCT04338061 (evolutionRMS 1 and evolutionRMS 2, target 898 patients each)	RRMS	Evobrutinib vs teriflunomide	ARR, EDSS progression, physical function, lesion formation	Recruiting; estimated completion June 2026
Tolebrutinib Sanofi	Phase 2b, RDB NCT03996291 (125 patients)	RRMS	Tolebrutinib vs placebo	AEs, lesion formation, ARR	Active, not recruiting; estimated completion April 2025; FDA hold placed in 2022
	Phase 3, RDB NCT04410978/NCT04410991 (GEMINI 1 and GEMINI 2, target 900 patients each)	RRMS	Tolebrutinib vs teriflunomide	ARR, disability worsening, lesion formation, brain volume loss	Active, not recruiting; estimated completion September 2023; FDA hold placed in 2022
	Phase 3, RDB NCT04411641 (HERCULES, target 1290 patients)	SPMS	Tolebrutinib vs placebo	Disability progression, physical function, lesion formation, brain volume loss, safety	Active, not recruiting; estimated completion August 2024 ; FDA hold placed in 2022
	Phase 3, RDB NCT04458051 (PERSEUS, target 990 patients)	PPMS	Tolebrutinib vs placebo	Disability progression, physical function, lesion formation, brain volume loss, safety	Active, not recruiting; estimated completion August 2024; FDA hold placed in 2022
Fenebrutinib Hoffmann-La Roche	Phase 2, RDB NCT05119569 (FENopta, target 102 patients)	RRMS	Fenebrutinib vs placebo	Lesion formation, AEs	Recruiting; estimated completion September 2024
	Phase 3, RDB NCT04586023/NCT04586010 (FENhance, target 736 patients)	RRMS	Fenebrutinib vs teriflunomide vs placebo	ARR, disability progression, lesion formation, brain volume loss	Recruiting; estimated completion November 2025
	Phase 3, RDB NCT04544449 (FENtrepid, target 946 patients)	PPMS	Fenebrutinib vs ocrelizumab vs placebo	Disability progression, brain volume loss, AEs	Recruiting; estimated completion December 2026
Orelabrutinib Biogen/Beijing InnoCare Pharma Tech	Phase 2, RDB NCT04711148 (target 160 patients)	RRMS	Orelabrutinib vs placebo	Lesion formation, AEs, ARR	Recruiting; estimated completion March 2024; FDA hold placed in 2022
Remibrutinib Novartis	Phase 3, RDB NCT05147220 (target 800 participants)	RRMS	Remibrutinib vs teriflunomide	ARR, EDSS progression, safety	Recruiting; estimated completion November 2029

AEs, adverse effects; ARR, annualized relapse rate; BTK, Bruton tyrosine kinase; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RDB, randomized double-blind; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

ΤΑ ΓΕΓΟΝΟΤΑ

- There are currently five BTK inhibitors in Phase III clinical trials for either relapsing or progressive MS: Sanofi’s tolebrutinib, Roche’s fenebrutinib, Novartis’ remibrutinib, InnoCare’s orelabrutinib, and Merck KGaA’s evobrutinib.
- Both tolebrutinib and orelabrutinib have had partial clinical holds (holds on new enrollment) placed by the FDA due to raised liver enzymes and potential liver injury, as did evobrutinib in April 2023 and fenebrutinib in December 2023.



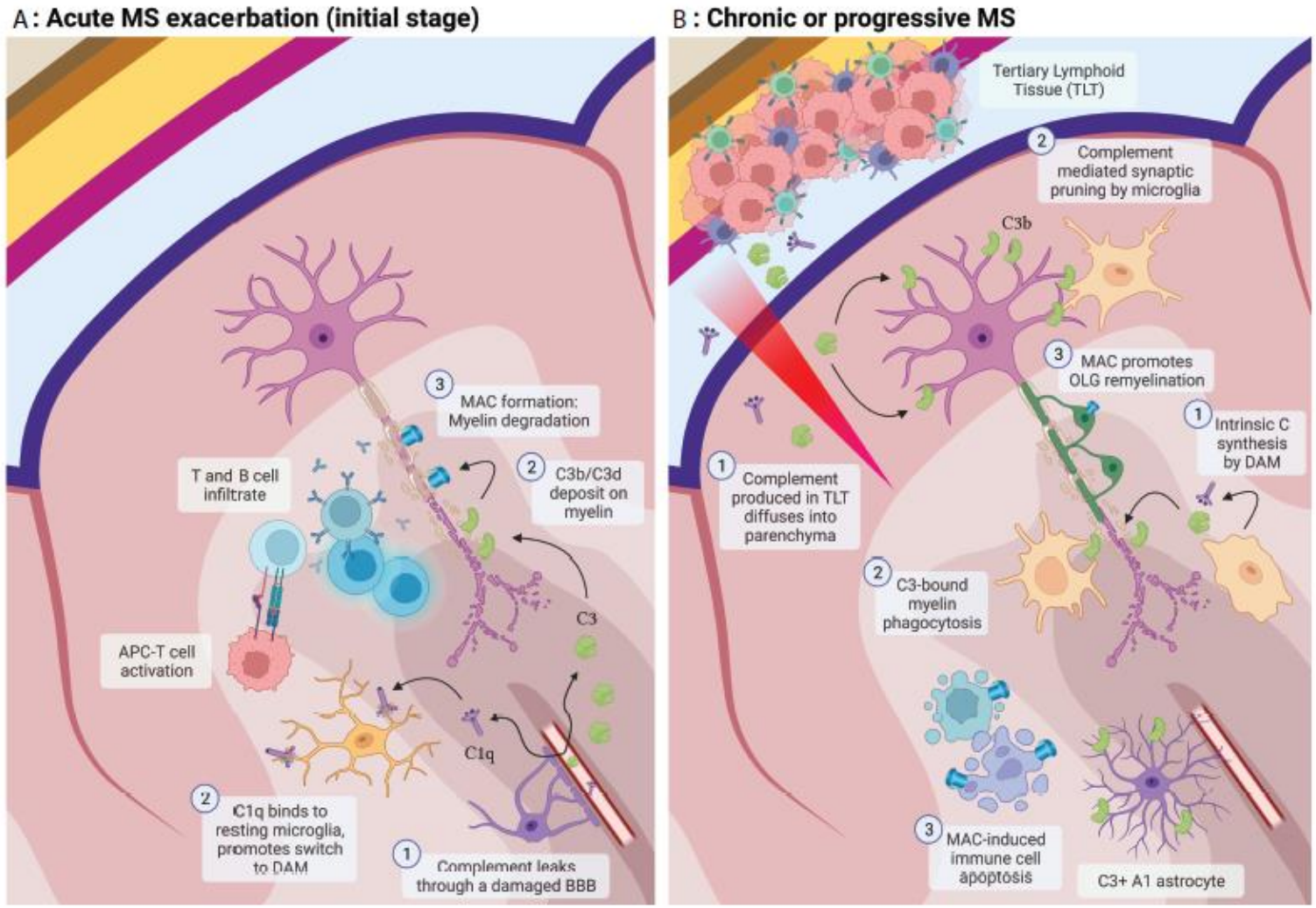
The role of the complement system in Multiple Sclerosis: A review

Front. Immunol. 13:970486.
doi: 10.3389/fimmu.2022.970486

Nil Saez-Calveras[1] and Olaf Stuve[1,2*]

(A) Acute MS exacerbation:
1. Complement factors leak through a compromised BBB. T and B cells infiltrate the parenchyma and are activated by myeloid APCs.
2. Activated C3b and C3d deposit on myelin promoting its opsonization. C1q binds resting microglia and modulates its phenotype switch to disease-associated microglia (DAM).
3. Downstream activation of complement leads to MAC formation and damage to the myelin membrane.

(B) Progressive MS:
1. Complement and other factors are secreted by DAM and by the tertiary lymphoid tissue (TLT) and diffuse into the brain parenchyma.
2. C3-bound myelin products are opsonized by myeloid cells and activated microglia.
3. In this stage, MAC formation exerts protective effects through the apoptosis of inflammatory cells and prevention of OLG apoptosis



frontiers in Cellular Neuroscience

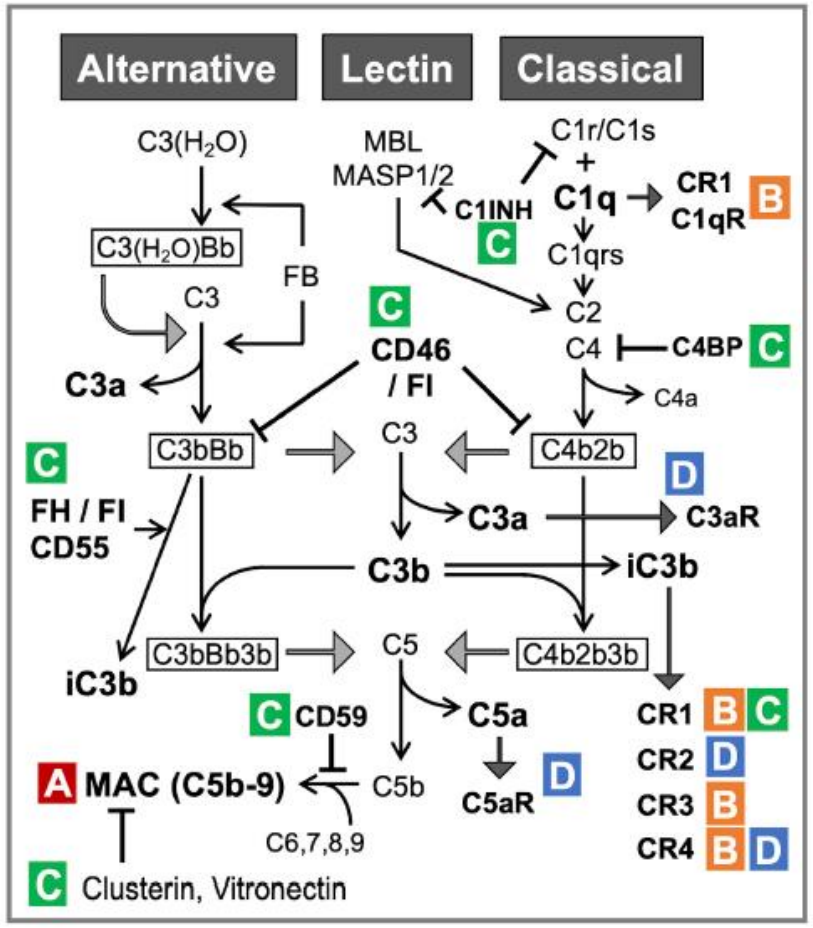
REVIEW
published: 02 August 2021
doi: 10.3389/fncel.2021.710390

Interaction Between the Complement System and Infectious Agents – A Potential Mechanistic Link to Neurodegeneration and Dementia

Noriko Shinjyo[1,2], Wataru Kagaya[3] and Marcela Pekna[4,5]*

ACTIVATION MODE

Classical: antibodies and antigens
Lectin: Lectins and sugars
Alternative: Pathogens and damaged tissue



Functions

A Cell lysis
Killing of pathogens

B Opsonization / Phagocytosis
- Clearance of apoptotic cells and debris (CR1/CR3/CR4/C1qR)
- Synaptic pruning (CR3)

C Regulation
Inhibition of the complement cascade

D Other functions
- Promotion of cell differentiation and recruitment (C3aR/C5aR)
- Modulation of immune cell migration (C3aR)
- Regulation of B-cell functions (CR2)
- Leukocyte adhesion (CR4)

The complement system is an evolutionarily conserved proteolytic cascade, consisting of over 40 components

Complement plays a key role as part of innate immunity, eliminating pathogens and damaged cells, directly killing bacteria by forming the so-called **membrane attack complex (MAC)**, and promoting inflammatory responses via the generation of **anaphylatoxins**

The activation of the complement system can be triggered via three pathways: the classical pathway, the lectin pathway, and the alternative pathway

Each of the activation pathways leads to the formation of C3 convertase (C4bC2b or C3bBb) that cleaves the third complement component (C3) into the C3a and C3b fragments.

In the next step of the activation cascade, we have the proteolytic cleavage of C5. C5 activation results in the release of C5a and the formation of **MAC**, a.k.a. the terminal complement complex, C5b-9.

C3a and C5a are peptides with **anaphylatoxin** properties and function as fluid-phase inflammatory mediators. They exert their biological
effects mainly through membrane-bound receptors. These receptors can propagate proinflammatory signals to induce cytokine/chemokine release and mediate the chemoattraction and activation of neutrophils and macrophages

The role of the complement system in Multiple Sclerosis: A review

Front. Immunol. 13:970486.
doi: 10.3389/fimmu.2022.970486

Nil Saez-Calveras[1] and Olaf Stuve[1,2]*

Currently available complement inhibitors used in clinical trials of neurologic and non-neurologic diseases

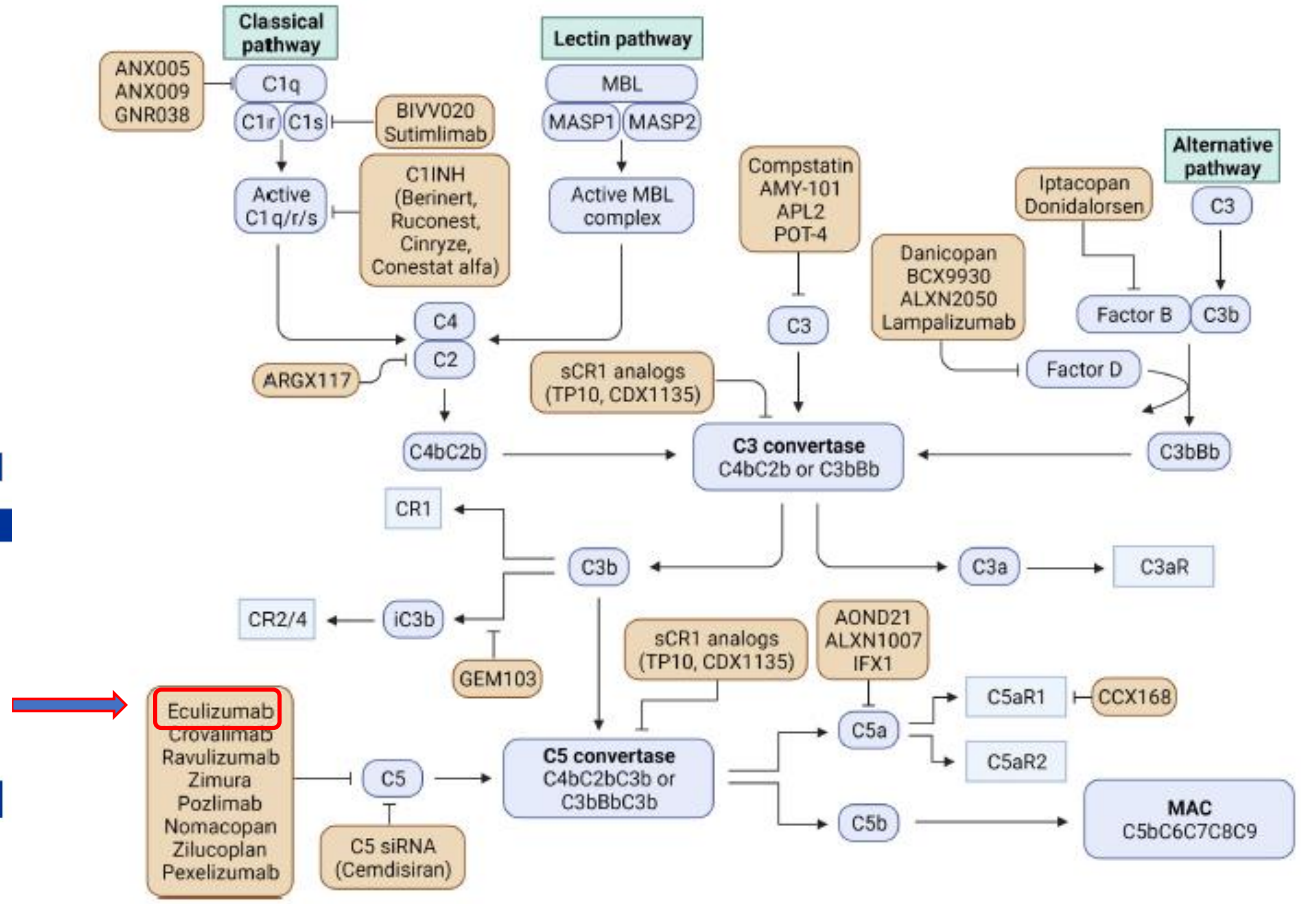


FIGURE 2
Currently available complement inhibitors used in clinical trials of neurologic and non-neurologic diseases (Created with BioRender.com).

The role of the complement system in Multiple Sclerosis: A review

Front. Immunol. 13:970486.
doi: 10.3389/fimmu.2022.970486

Nil Saez-Calveras[1] and Olaf Stuve[1,2]*

Effects of complement inhibition in MS animal models.

Inhibition	Animal model	Effect
C1q -/-	MOG_{35-55} induced EAE mice	Density of Iba1+ cells, microglia with reactive gliosis morphologies, expression of DAM marker CLEC7A lower in C1q -/- mice. No effect on disease phenotype [138]
ANX-M1.21 (C1q blocking antibody)	MOG_{35-55} induced EAE mice	Decreased Iba1+ and Iba1+/FTL+ microglia [138]
CVF (depletes C3)	Myelin + CFA immunized Lewis rats	CVF given at day 9 delayed onset of EAN by 2-3 days, when given at days 9-12 delayed onset by 4-5 days [132]
	BPN myelin immunized rats	Lower clinical scores, less demyelination. Fewer ED1-positive macrophages, CD11bc-positive cells [133]
C3-/-	MOG_{35-55} induced EAE mice	In both C3 -/- and factor B -/- mice, little infiltration of the parenchyma by macrophages and T cells, protection from demyelination [135]
		Mice equally susceptible to EAE. No differences in production of proinflammatory cytokines (IL-2, IL-4, IL-12, TNF-a, and IFN-γ) [136]
CR2-Crry	MOG_{35-55} induced EAE mice	Synaptic preservation in LGN where CR2-Crry AAV injected. Reduced synaptic terminal engulfment within microglial lysosomes. Visual acuity preservation. No effect on demyelination, axonal loss, gliosis, myelin engulfment [57]
		Administration prior to and during onset of EAE attenuates both MOG-induced and transferred EAE in CR2-Crry and CR2-factor H treated mice [99]
C3aR -/- C3a CNS expression	MOG_{35-55} induced EAE mice	C3aR -/- attenuated chronic EAE, modestly reduced macrophage and T cell infiltrates in the SC. Selective C3a-GFAP expression exacerbated chronic EAE, mortality, increased macrophage and T cell infiltrates [172]
Dual C3aR -/- C5aR -/-	MOG_{35-55} induced EAE mice	Delayed onset of disease but no attenuation of disease severity. Greater infiltration of CD4+ T cells [173]
C5aR -/-	MOG_{35-55} induced EAE mice	Mice fully susceptible to MOG-induced EAE, no difference in disease onset or severity. Similar macrophage and T cell infiltrates. Equal proinflammatory gene expression [171]
C5 -/-	Guinea pig myelin + incomplete Freund's adjuvant immunized mice	*Acute EAE:* Delay in inflammatory cell infiltrates and tissue damage *Chronic EAE:* Axonal depletion and severe gliosis in C5 -/-. Extensive remyelination in C5-sufficient mice [146]
	Myelin-induced EAE mice	Increased TUNEL + apoptotic cells in C5 -/- mice during clinical recovery (lymphocytes, monocytes, OLG) [147]
PMX205 (C5aR1 inhibitor)	Biozzi AB/H mice (syngeneic Biozzi AB/H spinal cord homogenate + CFA)	Amelioration of progressive neurological disability (not complete rescue). Reduction of NLPR3 inflammasome, upregulation of PPAR [143]
AcF-[OPdChaWR] (C5aR inhibitor)	*EAE:* gpBMP + CFA immunized rats *ADEAE:* Additional injection of Z12 (anti-myelin) mAb	Neutrophil response to C5a blocked. No effect on clinical disease or pathology [170]

Major difficulty: poor penetration of closed BBB- Techniques to overcome this obstacle

Case Report

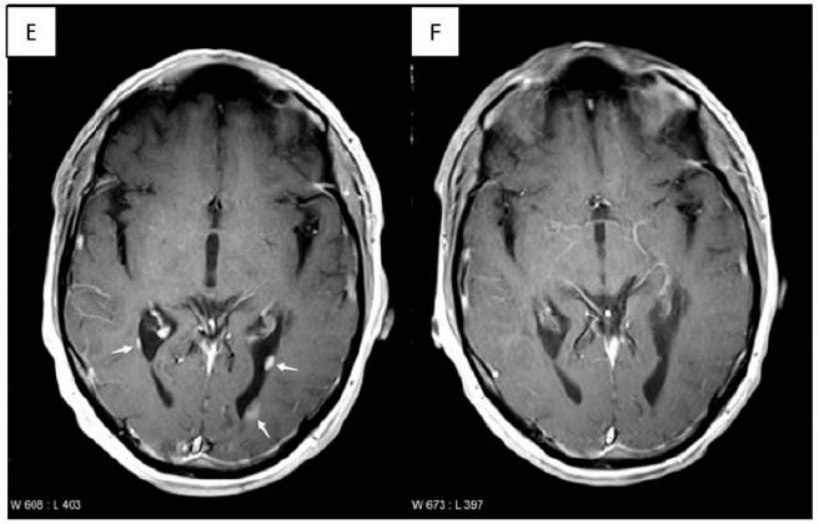
MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
2014, Vol. 20(11) 1541–1544

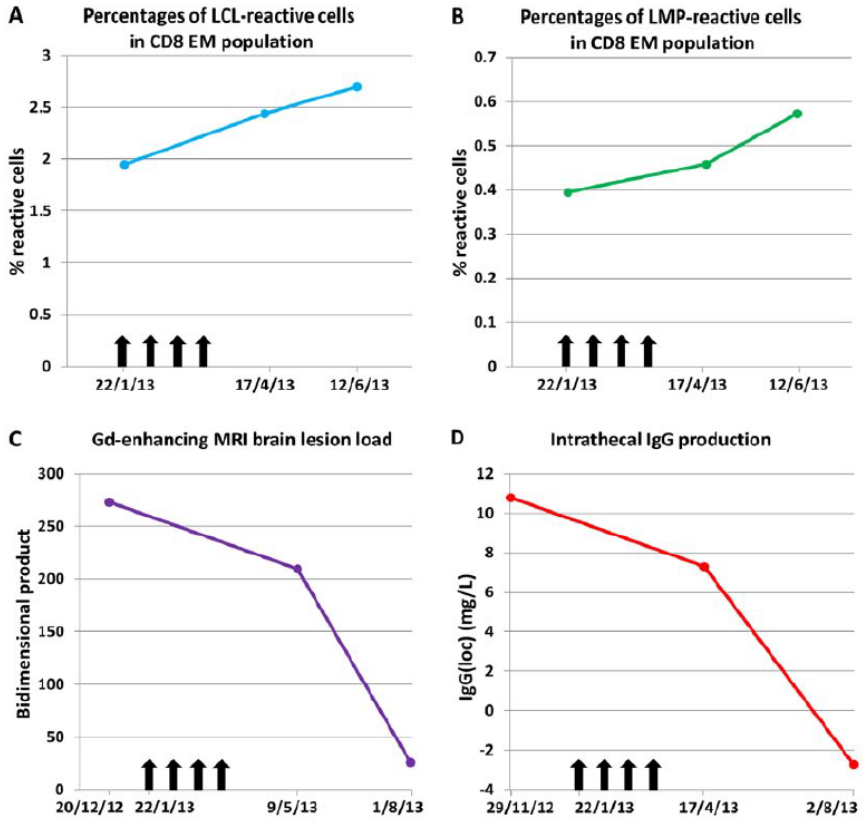
DOI: 10.1177/1352458514521888
msj.sagepub.com
SAGE

Epstein–Barr virus-specific adoptive immunotherapy for progressive multiple sclerosis

Michael P Pender[1–3], Peter A Csurhes[1,4], Corey Smith[3], Leone Beagley[3], Kaye D Hooper[1,2], Meenakshi Raj[2], Alan Coulthard[1,5], Scott R Burrows[1,3] and Rajiv Khanna[1,3]



- It has been hypothesized that defective elimination of EBV-infected B cells by cytotoxic CD8+ T cells predisposes to MS by allowing EBV-infected autoreactive B cells to accumulate in the central nervous system (CNS).
- This hypothesis predicts that adoptive immunotherapy to boost EBV-specific CD8+ T-cell immunity might be an effective treatment for MS.
- AdE1-LMPpoly is a novel recombinant adenovirus vector encoding multiple CD8+ T-cell epitopes from three EBV latent proteins, namely EBV nuclear antigen-1 (EBNA1), latent membrane protein 1 (LMP1) and LMP2A.
- Because EBV-infected B cells in the brain in MS express the same three EBV proteins, adoptive immunotherapy with AdE1-LMPpoly might be an effective way to increase the number of CD8+ T cells available to eliminate EBV-infected B cells from the CNS.



Long-term disability improvement during EBV-targeted T-cell immunotherapy ATA188 is related to brain volume change and normalised magnetisation transfer ratio in T2 lesions

November 08, 2023 05:35 PM Eastern Standard Time

THOUSAND OAKS, Calif.--(BUSINESS WIRE)--Atara Biotherapeutics, Inc. (Nasdaq: ATRA), a leader in T-cell immunotherapy, leveraging its novel allogeneic Epstein-Barr virus (EBV) T-cell platform to develop transformative therapies for patients with cancer and autoimmune diseases, today announced primary analysis data from its Phase 2 EMBOLD study of ATA188 in non-active progressive multiple sclerosis (PMS). The study did not meet the primary endpoint of confirmed disability improvement (CDI) by expanded disability status scale (EDSS) at 12 months compared to placebo. In addition, fluid and imaging biomarkers did not provide further supportive evidence.

assessed on T1-weighted MRI. nMTR evolution was measured within baseline unenhancing T2 lesions.

Results: 9/24 pts treated with ATA188 achieved sustained disability improvement (SDI) in the initial 12-month period or in the OLE; in 7/9, SDI was driven by EDSS (CDI). As of the most recent data provided, 5/5 pts with CDI remaining in the OLE maintained improvement for a median of 23.5 (range, 16.4–24.7) months. Safety in the OLE was consistent with previous reports. At 12 months, pts achieving SDI (vs not) during the study had significantly less enlargement of ventricular volume (PVVC; p=0.019) but similar PBVC and TVC. Similar trends were observed in pts achieving CDI (vs not). Longitudinal MRI analyses including OLE data showed that pts achieving CDI (vs not) had significantly higher nMTR over time (β=0.14, p=0.005), suggesting increased myelin density. Further, PBVC in pts achieving CDI (vs not) showed less decrease over time (β=0.34,p=0.037) and there was a trend for less ventricular volume enlargement over time (PVVC); TVC did not differ by CDI status.

Conclusion: Pts achieving CDI continuing in the OLE sustained CDI for up to 39 months. CDI was associated with less severe brain atrophy at 12 months and increasing nMTR in chronic T2 lesions over time, suggesting that brain structural changes, potentially including remyelination, persist over time and may underlie the CDI associated with ATA188.

39 μήνες μετά τη χορήγηση Ανοσοθεραπείας με ενεργοποιημένα Τ-λεμφοκύταρα (ATA188) παρατηρείται σταθερή βελτίωση της αναπηρίας με μειωμένη εγκεφαλική ατροφία και αυξημένο σήμα στην εξέταση με MTR στις Τ2 εστίες, ενδεικτικό πιθανής επαναμυελίνωσης!

Trial record **1 of 1** for: NCT04047628

Previous Study | Return to List | Next Study

Best Available Therapy Versus Autologous Hematopoetic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS) (BEAT-MS)

ClinicalTrials.gov Identifier: NCT04047628

Recruitment Status : Recruiting
First Posted : August 7, 2019
Last Update Posted : March 3, 2023

See Contacts and Locations

Condition or disease	Intervention/treatment
Relapsing Multiple Sclerosis	Procedure: Autologous Hematopoietic Stem Cell Transplantation
Relapsing Remitting Multiple Sclerosis	Biological: Best Available Therapy (BAT)
Secondary Progressive Multiple Sclerosis	

Participant recruitment for this six-year research study focuses on multiple sclerosis (MS) that has remained active despite treatment. This study will compare high dose immunosuppression followed by autologous hematopoietic stem cell transplantation (AHSCT) to best available therapy (BAT) in the treatment of relapsing MS.

Ακόμα μέχρι και σήμερα δεν έχουμε αποτελεσματικές θεραπείες στην προοδευτική πορεία της νόσου, συμπεριλαμβανομένης και της σιωπηλής προόδου που εκδηλώνεται στην υποτροπιάζουσα μορφή και είναι ανεξάρτητη των υποτροπών (PIRA).

Η μερική αποτελεσματικότητα των θεραπειών κατά των Β-λεμφοκυτάρων (Rituximab, Ocrelizumab, Ofatumumab) στην προοδευτική πορεία της νόσου, οδήγησε στην προσπάθεια χορήγησης μεγαλύτερων δόσεων ή και πρώιμη έναρξη θεραπείας με πολύ αποτελεσματικά φάρμακα ώστε να αποτραπεί η δημιουργία ανθεκτικών στη θεραπεία συσσωρεύσεων Β-λεμφοκυττάρων τα οποία οδηγούν σε χρόνια νευροεκφύλιση πίσω από ένα κλειστό αιματεγκεφαλικό φραγμό (διαμερισματοποίηση)

Μια άλλη υποσχόμενη, παρά τις αρχικές δυσκολίες, περιοχή έρευνας αποτελούν οι αναστολείς της Τυροσινικής Κινάσης Bruton (BTK-Inhibitors) και οι πολύ πρόσφατα δοκιμαζόμενοι αναστολείς των παραγόντων του συμπληρώματος ουσίες οι οποίες και οι δύο αναστέλλουν τη δράση τόσο των Β-λεμφοκυτάρων όσο και της μικρογλοίας.

Η πολύ ισχυρή συσχέτιση του ιού EBV στην παθογένεση της Πολλαπλής Σκλήρυνσης μας οδηγεί στην ανάπτυξη καινοτόμων θεραπειών είτε προς την εξάλειψη του ιού από τα μολυσμένα Β-λεμφοκύταρα ή προς την εκλεκτική θανάτωση των Β-λεμφοκυτάρων που περιέχουν μέσα τους γενετικό υλικό του ιού EBV

Τέλος, θεραπείες νευρο-αποκατάστασης οι οποίες θα μπορούν να μειώσουν ή και να αναστρέψουν την αναπηρία μέσω διορθωτικών μηχανισμών, όπως: επαναμυελίνωσης, αξονικής αναγέννησης ή και νευρογένεσης αρχίζουν σιγά-σιγά να εμφανίζονται στο προσκήνιο

Ευχαριστώ για την προσοχή σας

Ερωτήσεις??